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Pathophysiology of vestibular neuropathy

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Pathophysiology of vestibular neuropathy

zur Erlangung der Venia legendi der Universität Zürich

vorgelegt von
Antonella Palla, Dr. med.
Zürich, 2009

Zusammenfassung der Habilitationsschrift:

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3. Palla A, Straumann D, Bronstein AM (2008) Vestibular neuritis: vertigo and the high-acceleration vestibulo-ocular reflex. J Neurol 255: 1479-1482
4. Jorns-Häderli M, Straumann D, Palla A (2007) Accuracy of the bedside head impulse test in detecting vestibular hypofunction. J Neurol Neurosurg Psychiatry 78: 1113-1118
5. Palla A*, Schmid-Priscoveanu A*, Studer A, Hess K, Straumann D (2009) Deficient high-acceleration vestibular function in polyneuropathic patients. Neurology 72: 2009-2013
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7. Palla A, Hegemann S, Widmer U, Straumann D (2007) Vestibular and auditory deficits in Fabry disease and their response to enzyme replacement therapy. J Neurol 254: 1433-1442
8. Palla A, Widmer U, Straumann D (2003) Head-impulse testing in Fabry disease - vestibular function in male and female patients. Acta Paediatr Suppl 443: 38-42

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Introduction

With a prevalence in the general population of about 30%, vertigo and dizziness are not only common morbidity causes, but also have a large impact on the individual's life as half of the patients affected by dizziness change or give up their jobs (1).

The second most frequent cause of peripheral-vestibular vertigo is vestibular neuritis (VN). It is defined as a sudden unilateral deficit of the peripheral vestibular organ (labyrinth or nerve) without auditory symptoms in otherwise healthy persons and most likely has a viral etiology (2-4).

During acute VN, patients avoid lying on their affected ear, because this intensifies the vertigo. In fact, the horizontal spontaneous nystagmus increases in this position, indicating nystagmus modulation by gravity (5). Signs and symptoms of static vestibular imbalance usually disappear within one week. Recovery of dynamic vestibular imbalance, however, differs depending on the stimulation frequency (6). While the low-frequency peripheral vestibular function, as tested by caloric irrigation, often recovers or becomes symmetrical (7-9), the impairment in the high-frequency range does not, as assessed by head impulses or head-shaking (10-12). It remains unclear, however, whether this deficit decreases over time indicating peripheral recovery and/or central compensation. When VN becomes chronic, almost 50% of patients report sustained dizziness (13-16), though vestibular function does not differ between symptomatic and symptom-free patients when assessed by caloric irrigation, rotatory chair testing, posturography, or clinical balance testing (13, 15-17). This might be due to the fact that these tests measure only the low-frequency components of vestibular function.

The main clinical question in patients with vertigo is whether the lesion is peripheral (e.g. VN) or central (e.g. brainstem or cerebellar stroke), the latter requiring immediate neuroimaging. The head impulse test is useful in this situation, because it will almost exclusively be positive in patients with VN (note, however, that ischemic infarctions along the entry zone of the eighth nerve or vestibular nucleus can rarely mimic VN, so-called vestibular pseudoneuritis (18)). So far, the accuracy of the head impulse test as a bedside examination of peripheral vestibular function has only been established in reference to caloric irrigation (19, 20). Direct comparison of both tests, however, is problematic, as head impulses and caloric irrigation probe different frequencies of vestibular function. Moreover, central compensation mechanisms in response to a peripheral vestibular deficit are frequency dependent and more often incomplete for higher (head impulses) than for lower frequencies (caloric irrigation) (7-12).

It is generally assumed that postural imbalance in patients with polyneuropathy (PNP) result from reduced somatosensory input to the brain from the distal part of the legs. The question is whether a vestibular nerve neuropathy could also play a role. The recognition of a vestibular impairment is pivotal, because therapeutic strategies focusing on vestibular rehabilitation can improve postural stability (21). Fabry disease, an X-linked lysosomal storage disorder, is characterized by a progressive peripheral neuropathy (22). Here also, the prevalence of an additional vestibular impairment is unknown.

In order to answer the questions elaborated above, a series of studies were conducted in vestibulopathic patients aiming to: (1) investigate the peripheral recovery and/or central compensation and the influence of gravity on the high-frequency peripheral vestibular function in VN, (2) correlate persistent vestibular symptoms with peripheral vestibular function in VN, (3)

assess the accuracy of the bedside head impulse test in VN, and (4) determine the prevalence of vestibular impairment in unselected PNP-patients and in patients with Fabry disease.

Materials and Methods

Study 1: The asymmetry of the high-frequency peripheral vestibular function over time was investigated in 37 patients 1-240 weeks after VN onset by recording with search coils the horizontal vestibulo-ocular reflex (VOR) during horizontal head impulses to both sides (so-called quantitative head impulse testing – qHIT).

Study 2: The influence of gravity on head-shaking nystagmus in 7 chronic VN patients was investigated using a three-dimensional turntable. Patients were placed in different whole-body roll positions and oscillated (1Hz, $\pm 10^\circ$) about their head-fixed vertical axis. Eye movements were recorded with search coils.

Study 3: Persistent symptoms in 47 patients with VN were correlated with sustained impairment of the horizontal VOR as determined by qHIT 1 week to 60 months after VN onset. Symptom severity was assessed with the Yardley Vertigo Symptom Scale short form ≥ 18 months after VN onset.

Study 4: The accuracy of the bedside head impulse test (bHIT) was determined by intra-individual comparison with the qHIT. The horizontal bHIT to both sides was performed on nine patients with unilateral and bilateral peripheral vestibular deficits and nine healthy subjects and videotaped. Clinicians with ≥ 6 months of neuro-otological training ('experts': $n=12$) or without training ('non-experts': $n=45$) assessed the video for ocular motor signs of vestibular deficits.

Study 5-6: To investigate whether polyneuropathic processes impair vestibular function, the qHIT was performed in 37 patients (mean age: $65y \pm 12SD$) with electrodiagnostically confirmed PNP (predominantly axonal: 18; predominantly demyelinating: 19).

Study 7-8: The prevalence of peripheral vestibular deficit and the association to hearing loss was studied in 24 male (18–60y) and 22 female (17–74y) patients with Fabry disease and the effect of enzyme replacement therapy on peripheral vestibular function was assessed using qHIT.

Results

Study 1 revealed that the gains of the horizontal vestibulo-ocular reflex (VOR) during head impulses toward the ipsilesional side significantly increased within one month after VN onset (average gains: <1 week: 0.35; 1–4 weeks: 0.33; 4–40 weeks: 0.55; 40–240 weeks: 0.50). Gains on the contralesional side were slightly but not significantly reduced. *Study 2* indicated that head-shaking nystagmus was modulated by gravity: When patients lay on the affected ear side, the slow-phase eye velocity significantly increased upon head shaking (average: $1.2^\circ/s \pm 0.5$ SD). *Study 3* found no correlation between the magnitude of the high-frequency vestibular impairment and the severity of vertigo symptoms. *Study 4* showed that, on average, bHIT sensitivity was significantly lower for experts than for non-experts (63% vs. 72%), while bHIT specificity was significantly higher for experts than non-experts (78% vs. 64%). *Studies 5-6* revealed that the high-frequency vestibular function was unilaterally ($\sim 50\%$) or bilaterally ($\sim 50\%$) impaired in two thirds of patients with axonal or demyelinating PNP. In the course of PNP progression, vestibular function deteriorated asymmetrically, first affecting one side and later both sides. Finally, *studies 6-7* found that 80% of male and 77% of female patients with Fabry

disease had an impaired vestibular function as determined by qHIT. The prevalence of the high-frequency vestibular impairment paralleled the hearing involvement. Enzyme replacement therapy stabilized the auditory function and even improved the vestibular function.

Discussion

We demonstrated that after VN, the ipsilesional high-frequency peripheral vestibular function improves over time (paper #1). Because this is not observed in patients with a permanent vestibular function loss (23-24), results suggest that the ipsilesional recovery is peripheral or, if central, depends on spared peripheral function. Interestingly, this finding is supported by a model of linear and non-linear vestibulo-ocular reflex pathways (paper #1) that also predicts a considerable gain reduction of the contralesional side, if central compensation mechanisms are not engaged. Since our study reported only a slight gain reduction of the contralesional side, we speculate that effective central compensation after VN does not aim to balance the peripheral vestibular function on the ipsi- and contralesional sides but tries to boost the peripheral vestibular function on the contralesional side close to normal.

We found a gravity dependence of head-shaking nystagmus in chronic VN patients, indicating an interaction between otolith and semicircular canal pathway signals (paper #2). This phenomenon might represent an asymmetric suppression of vestibular nystagmus due to the unilateral involvement of otolith organs or their afferents, similarly to what happens with the spontaneous nystagmus in patients with acute VN. It is important to emphasize that persistent dizziness and vertigo symptoms after VN are not significantly associated with sustained vestibular impairment as shown by testing both the low-frequency as well as the high-frequency vestibular function (13, 15-17 and paper #3). The lack of association between the severity of symptoms and the outcome of the vestibular function tests might suggest that the persistent vertigo and dizziness in VN patients could be due to inappropriate cortical adaptation mechanisms, including psychophysical processes.

Previous reports found the bedside head impulse test (bHIT) insensitive to mild or moderate vestibular loss (19-20). However, comparison of the bHIT with the qHIT, showed that bHIT sensitivity is adequate (~70%) and therefore clinically useful in the hands of both neuro-otological experts and non-experts (paper #4). This finding is even more important when considering the surprisingly high percentage of vestibular impairment found in ~70% of patients with polyneuropathy due to the involvement of the vestibular nerve, which deteriorates asymmetrically over time first on one side and later on both sides (papers #5 and 6). This finding is highly relevant and should prompt clinicians to routinely assess bHIT in PNP patients for a timely prescription of physical therapy. The same holds for patients with Fabry disease. Interestingly, and contrary to previous reports, the prevalence of vestibular damage in Fabry disease, as assessed by qHIT, parallels the prevalence of hearing impairment. Moreover, the qHIT had a higher sensitivity than caloric irrigation for detecting vestibular impairment (papers #8 and 9). We speculated that hearing and vestibular damage emerge from lesions within the labyrinth, because of no evidence of specific patterns of vestibulo-cochlear deficits, as would be expected if lesions were more proximal along the inferior or superior branch of the vestibulo-cochlear nerve or the labyrinthine artery. Finally, enzyme replacement therapy stabilized auditory and even improved vestibular function.

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Recovery of the High-Acceleration Vestibulo-ocular Reflex After Vestibular Neuritis

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ABSTRACT

Vestibular neuritis (VN) usually leads to a sudden gain asymmetry of the high-acceleration horizontal vestibulo-ocular reflex (VOR). We asked whether this asymmetry decreases over time indicating peripheral recovery and/or central compensation. The horizontal VOR during rapid rotational head impulses to both sides was recorded with search coils in 37 patients at different time periods (1–240 weeks) after the onset of VN. In ten patients, sequential measurements were performed. Gains of the VOR during head impulses toward the ipsilesional side significantly increased after the initial drop (average gains: < 1 week: 0.35; 1–4 weeks: 0.33; 4–40 weeks: 0.55; 40–240 weeks: 0.50). Gains on the contralesional side, however, were only slightly reduced and showed no significant change. We conclude that, in contrast to patients after hemilabyrinthectomy or unilateral vestibular neurectomy, the ocular response to ipsilesional rotations in patients after VN improves over time. This finding suggests that ipsilesional recovery is peripheral or, if central, depends on spared peripheral function. The physiology of linear and non-linear VOR pathways predicts a considerable gain reduction for contralesional head impulses if central compensation mechanisms are not engaged. Thus, the relatively preserved gain on the contralesional side can be explained only by central “upregulation”. Apparently, for high accelerations of the head, effective central compensation after VN does not aim to balance the gains of the VOR but tries to boost the contralesional gain close to normal.

Keywords: neuro-otology, central compensation, VOR upregulation, head-impulse test, Ewald’s second law, VOR pathways

INTRODUCTION

Vestibular neuritis (VN) is a sudden unilateral deficit of the peripheral vestibular organ (labyrinth or nerve) without auditory symptoms in otherwise healthy persons and leads to both static and dynamic vestibular imbalances. Recent studies have suggested a viral etiology of VN (Schuknecht and Kitamura 1981), most likely a reactivation of latent herpes simplex virus type 1 (Furuta et al. 1993; Schulz et al. 1998; Arbusow et al. 1999, 2000).

Signs and symptoms of VN due to static vestibular imbalance, such as postural instability, sensation of rotation, and spontaneous horizontal nystagmus, usually disappear within one week (Brandt 2001). Recovery from dynamic vestibular imbalance after VN is frequency-dependent (Paige 1989). When tested with low accelerations used in clinical turntable testing or caloric irrigation, the gains of the vestibulo-ocular reflex (VOR) become symmetrical within several weeks (Brantberg and Magnusson 1990; Imate and Sekitani 1993; Allum and Ledin 1999). When tested with high accelerations generated by Halmagyi–Curthoys head impulses (Halmagyi and Curthoys 1988), however, the horizontal VOR often remains asymmetrical, even after many years (Schmid–Priscoveanu et al. 1999, 2001; Aw et al. 2001).

Patients with permanent unilateral vestibular loss due to vestibular neurectomy also show gain asymmetries of the horizontal VOR evoked by head im-

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pulses. In these patients, the magnitude of asymmetry does not change for many years (Halmagyi et al. 1990; Aw et al. 1996, 2001). Thus, a unilaterally absent peripheral function seems to be associated with a persistent gain asymmetry of the high-acceleration VOR. Conversely, an ipsilesional gain increase would indicate either incremental peripheral recovery or progressively more effective central compensation making use of the spared ipsilesional peripheral vestibular input. We asked whether, in fact, the gain asymmetry of the high-acceleration VOR after VN would decrease over time as a result of residual peripheral vestibular function.

After VN, the gain of the VOR evoked by contralateral head impulses is, on average, slightly below normal (Schmid-Priscoveanu et al. 1999; Aw et al. 2001). The same small contralesional gain reduction is also found in patients after unilateral vestibular neurectomy (Halmagyi et al. 1990; Aw et al. 1996, 2001). It is still unclear to what extent the unilateral peripheral deficit and central compensation mechanisms determine the gain on the contralesional side. Using a realistic model of the VOR (Lasker et al. 2000), we asked whether the contralateral gain reduction of the high-acceleration VOR in patients after VN can be explained by a unilateral deficit with or without central compensation mechanisms alone or whether, in some cases, an additional involvement of the contralateral labyrinth or vestibular nerve is likely.

MATERIAL AND METHODS

Subjects

Thirty-seven patients (21 male, 27–83 years old) diagnosed with vestibular deficit due to clinically suspected vestibular neuritis (VN) were included in the study. The patients were partitioned into four groups according to the time passed from the onset of the vestibular deficit to the date of the examination (group I: 1 day–1 week; group II: 1–4 weeks; group III: 4–40 weeks; group IV: 40–240 weeks). These intervals represent an approximate logarithmic distribution. Ten patients were assigned to two different groups, since they could be tested twice at different time periods after the onset of the deficit. The total number of testing sessions was 47 (group I: 6; group II: 6; group III: 11; group IV: 24). The comparison group consisted of 11 healthy human subjects (5 male, 25–39 years old).

Informed consent of patients and healthy subjects was obtained after full explanation of the experimental procedure. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declara-

tion of Helsinki for research involving human subjects.

Quantitative head impulse testing

Eye and head movements were recorded in a magnetic frame (Remmel-type system, modified by A. Lasker, Baltimore, MD, USA) using dual search coils (Skalar Instruments, Delft, Netherlands) that were calibrated before each session (for details see Straumann and Zee 1995). One search coil was placed on the right eye around the cornea (after anesthetizing the conjunctiva with oxybuprocaine 0.4%), the other was tightly fixed on the forehead with adhesive tape. Voltages were sampled with 16 bits at 1000 Hz and stored on the hard disk of a computer.

During experiments, subjects were seated inside the magnetic coil frame (side length = 1.4 m). Care was taken to position the center of the interpupillary line in the center of the magnetic frame. Horizontal head impulses (amplitude = 20°–40°; duration = 150–200 ms; peak velocity = ~300°/s; peak acceleration = ~10,000°/s²) were applied by the investigator standing behind the subject. The directions of head impulses were pseudorandomly intermingled; four to six head rotations were applied to each side. Subjects were instructed to always fix upon a light dot 1.24 m straight ahead.

Data analysis

Digitized signals were processed using interactive programs written in MATLAB (version 6.1). Since it is not known whether VN affects only the gain or, in addition, the latency of the vestibulo-ocular reflex, we used an analytical method that implicitly discards the effect of latency on the gain value.¹ This was achieved by plotting head-in-space against eye-in-space. The gain of the vestibulo-ocular reflex, g , was computed using the formula:

$$g = \frac{\Delta e_s[h_0; h_1]}{h_1 - h_0}$$

where h_0 and h_1 are head-in-space positions, and Δe_s is the difference between eye-in-space positions at $h_0 = 3^\circ$ and $h_1 = 7^\circ$. Traces of head impulses traversing the position interval $[h_0; h_1]$ were relatively straight. In every trial, this position interval was traversed after the moment of peak head acceleration and before the moment of peak head velocity.

¹Increased latency leads to a false reduction of gain, if determined at peak head velocity.

FIG. 1. Examples of horizontal head impulse tests in a healthy subject (**A**) and a patient two weeks (**B**) and two months (**C**) after a sudden vestibular asymmetry. If the vestibulo-ocular reflex (VOR) were perfectly compensatory, traces would be parallel to the abscissa (head-in-space axis); if the vestibulo-ocular reflex were absent, traces would move on a 45° slope. G_R : median gain value for head impulses to the right; G_L : median gain value for head impulses to the left. Traces are clipped beyond 10° eccentricity of head-in-space. Dashed vertical lines indicate intervals used to determine the gains (see Methods).

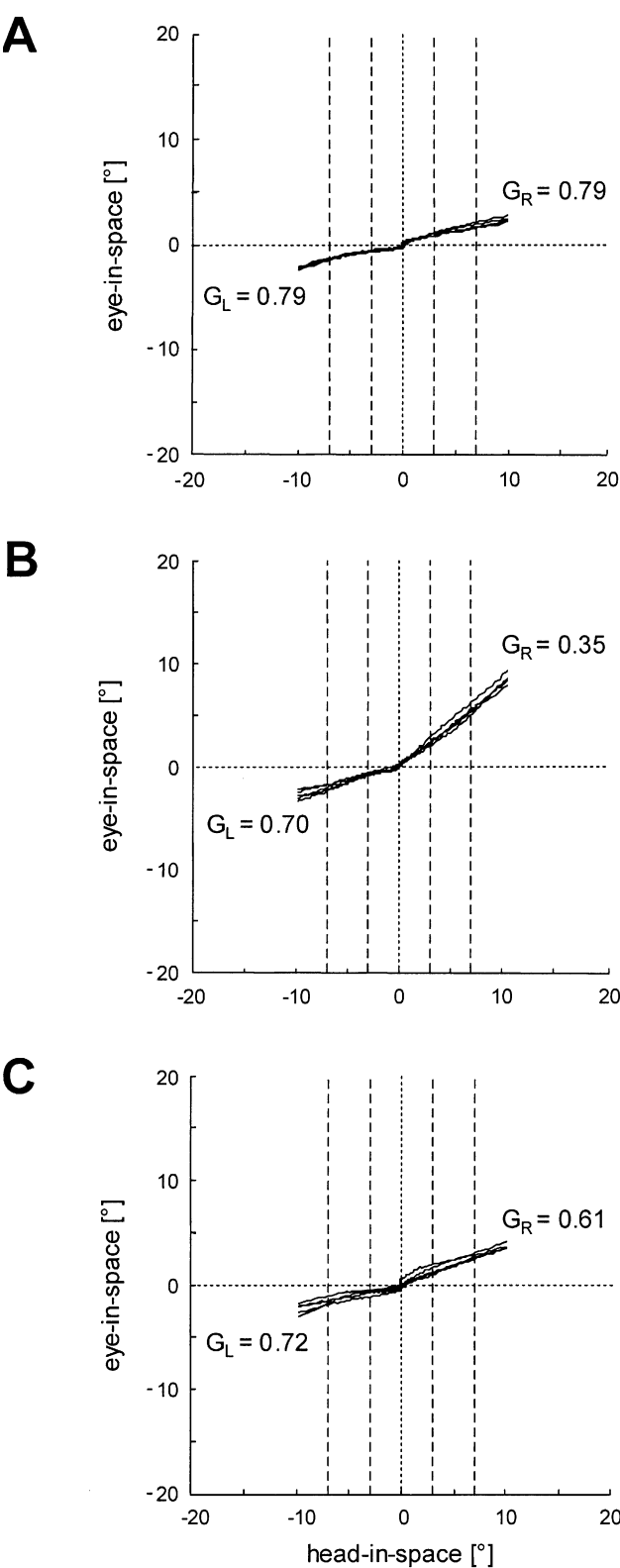
Median gains during head impulses to the right (G_R) and left (G_L) side were calculated. For convenience, the gains of patients and healthy subjects were mirrored, if the gain on the right side was higher than the gain on the left side. Thus, in the analysis of the patients' data, the right side is always ipsilesional and the left side contralesional.

RESULTS

Figure 1 contains three plots of head and eye movements during horizontal head impulses to both sides in a typical healthy subject (Fig. 1A) and a typical patient (Fig. 1B, C). In the healthy subject (Fig. 1A), gains were symmetric but not completely compensatory. In the patient, the gain for ipsilesional head impulses was markedly reduced two weeks after the onset of vestibular neuritis (Fig. 1B), while the contralesional gain was somewhat yet not significantly lower than gains in healthy subjects. The same patient was tested two months later (Fig. 1C). The ipsilesional gain had increased, and the contralesional gain was only slightly above the previous value. Hence, the difference between both gains became smaller.

Figure 2 plots average gain values of each group of patients during head impulses toward the ipsilesional (Fig. 2A) and the contralesional (Fig. 2B) side, as well as the difference between the two sides (Fig. 2C). During head impulses toward the ipsilesional side (Fig. 2A), average gain values were around 0.35 during the first week (group I) and subsequent three weeks (group II), but they then rose to a level of around 0.50 (groups III and IV). Gains measured during head impulses toward the contralesional side (Fig. 2B) were, on average, somewhat below normal values. The decrease, however, was not significant and also showed no significant change over time. Differences between ipsi- and contralesional gains (Fig. 2C) were around 0.35 during the first four weeks (groups I and II) and then decreased to around 0.2 (groups III and IV).

Ten patients could be tested twice at different time intervals after the onset of the vestibular deficit. Figure 3 illustrates the ipsi- and contralesional gain val-



ues of these patients in the same format as in Figure 2. Again, there was a clear tendency of the ipsilesional gain to improve over time (Fig. 3A), while the contralesional gain was slightly but not significantly below normal and stayed at that level (Fig. 3B).

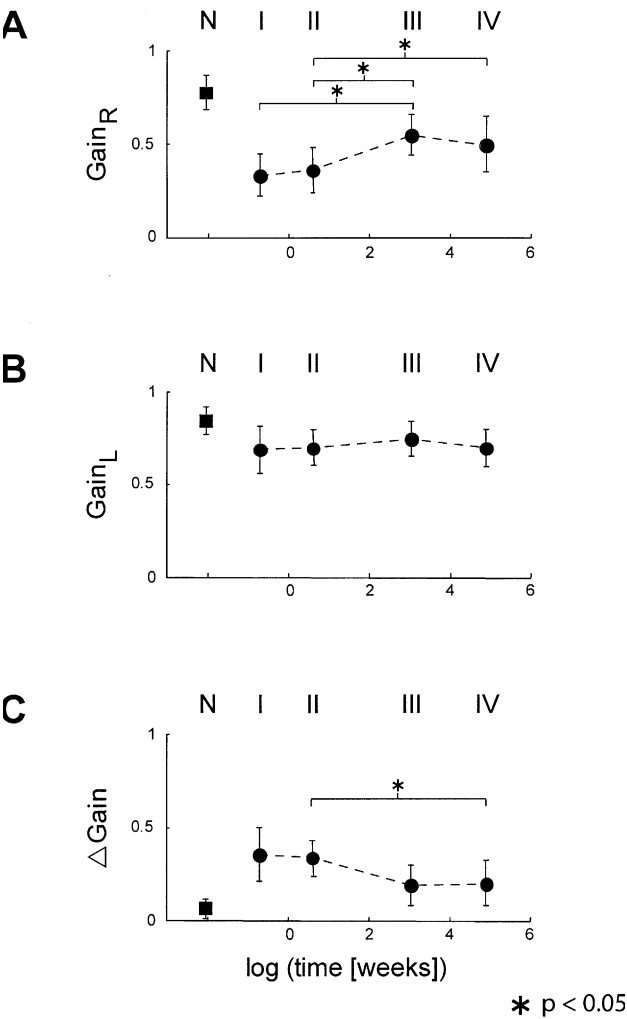


FIG. 2. Average gain values (error bars: ± 1 SD) of the four groups of patients (I, II, III, IV) and the group of healthy subjects (N). The abscissa indicates logarithmic time, except for the group of healthy subjects. In all panels, averages in the four groups of patients were significantly different from averages in the group of healthy subjects ($p < 0.05$ in the unpaired two-tailed t -test). Stars indicate significant differences of averages between patient groups. **A.** Head impulses toward the right side. **B.** Head impulses toward the left side. **C.** Gain differences (left minus right gain). Note that the gains were mirrored in subjects in whom the gain on the right side was higher than on the left side. Thus, the right side was always the weaker side and, as a result, the gain differences were always positive (see Methods).

As a consequence, the asymmetry between ipsi- and contralesional gains decreased as a function of time (Fig. 3C).

So far, we have shown that the gain of the VOR during head impulses toward the ipsilesional side partly recovered after the onset of the deficit. To interpret the gain values during head impulses toward the contralesional side, we compared our data with the predictions of a recent model by Lasker et al. (2000), which is based on ocular responses of hemilabyrinthectomized squirrel monkeys during high-frequency, high-acceleration rotations. In these ani-

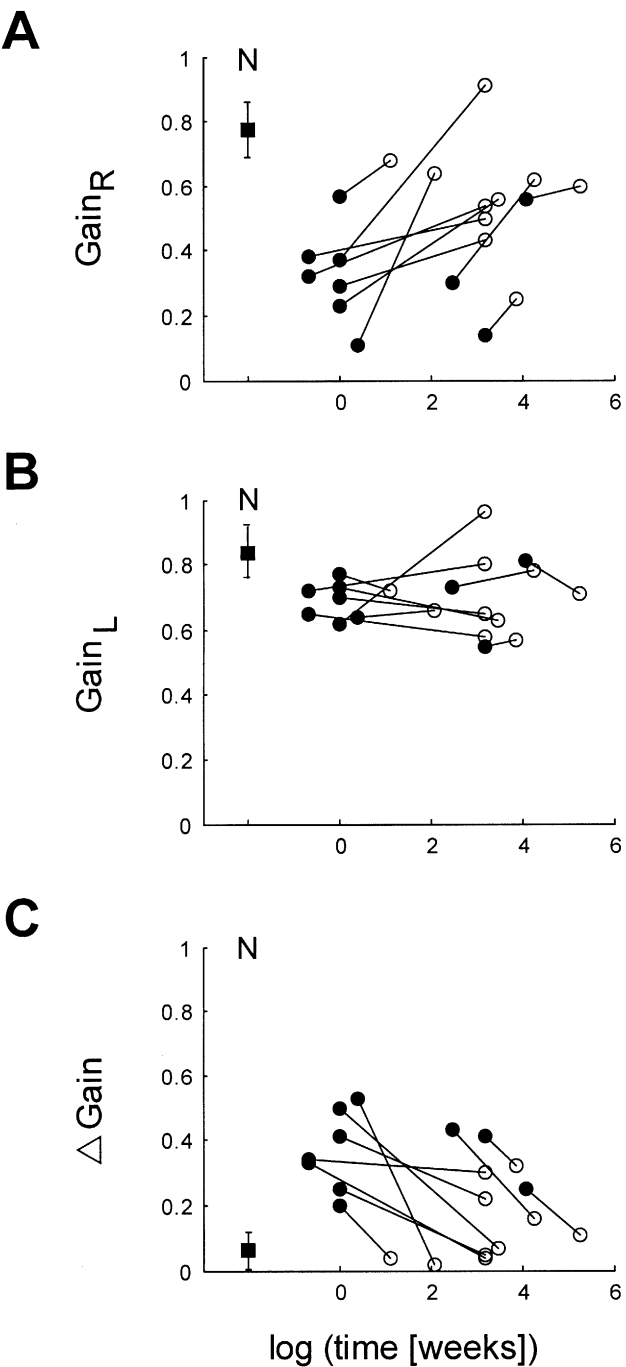


FIG. 3. Individual gain values in the ten patients who could be tested twice at different time periods after the onset of vestibular neuritis. Panels and scales are as in Figure 2. Filled circles: first measurements; open circles: consecutive measurements; filled square: average values in healthy subjects (error bars: ± 1 SD).

mals, the VOR gain was higher when the head was accelerated toward the contralesional side, but at the subsequent velocity plateau horizontal gains were symmetric. The mathematical model by Lasker et al. accounts for these properties by implementing a linear and a nonlinear pathway on both sides. Figure 4 summarizes the main features of this model.

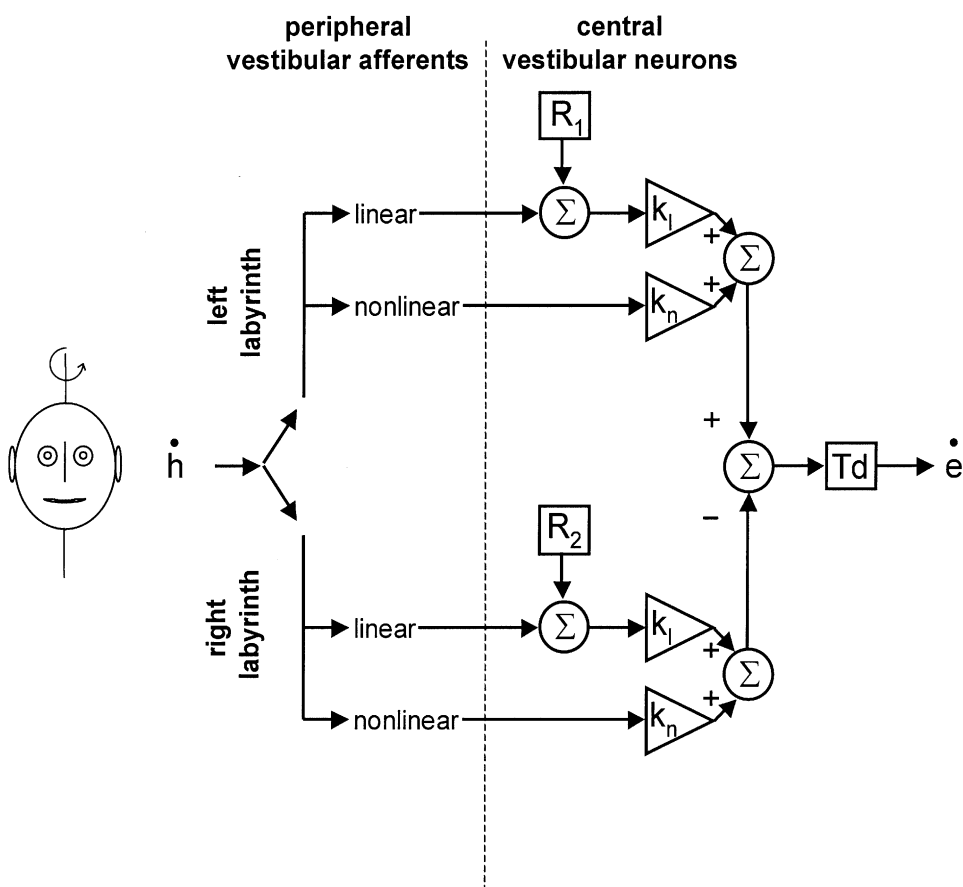


FIG. 4. Simplified diagram of the model described by Lasker et al. (2000). The input to the vestibulo-ocular reflex is angular head velocity (\dot{h}). This signal is passed through linear and nonlinear pathways. k_1 and k_n represent the corresponding central gain elements of these two pathways. R denotes the resting rate of central vestibular neurons, which is added to the linear pathway. T_d : time delay of the reflex (set to 7 ms in our simulations).

The responses of the reflex during sinusoidal rotation with low peak velocities ($< 30^\circ/\text{s}$) and during the velocity plateau after acceleration are attributed largely to the linear pathway that reacts relatively symmetrically upon labyrinthine inhibition and excitation. During sinusoidal rotation with higher frequencies and peak velocities, and during high-acceleration steps, there is an additional but relatively small gain contribution from the ipsilateral nonlinear pathway. For instance, during a typical head impulse (duration 0.4 s; amplitude = 40° ; peak velocity = $470^\circ/\text{s}$; peak acceleration = $12,000^\circ/\text{s}^2$), the gain contribution of the ipsilateral nonlinear pathway amounts to 11% according to the model. Therefore, a reduced vestibular signal from one labyrinth, e.g., after vestibular neuritis, will always result in an asymmetric gain during horizontal head impulses with the lower value during ipsilesional head rotation.

Lasker et al. (2000) found that in order to model the responses of hemilabyrinthectomized animals, they had to make the following adjustments in the model parameters: a decreased resting rate of ipsilateral central vestibular neurons (R) by 11%, an increased gain of the contralateral linear pathway (k_1) by 20%, and an increased gain of the contralateral nonlinear pathway (k_n) by 250%. With these changes,

which most likely are mediated by the central nervous system, the model does agree with the data obtained in the experimental animals. Note that in the context of the model, the term “gain” refers to a multiplication of an incoming signal, while for the behavioral description the VOR “gain” is defined by “eye velocity divided by head velocity”.

The performance of the model upon stimulations used in our study is illustrated in Figure 5. A representative head impulse, as measured with a search coil placed on the forehead, served as input to the model (Fig. 5A). A right-sided unilateral vestibular deficit was simulated by increasing the deficit of the right-sided input (Fig. 5BD) from 0% (thin solid line corresponding to a normal right-sided vestibular input) to 100% (thick solid line corresponding to a total right-sided vestibular loss) with increments of 10% (dashed lines). Without central changes (Fig. 5B), no spontaneous nystagmus appears, and the unilateral deficit reduces the gain of the VOR not only during ipsilesional but also during contralesional head impulses. The gain is reduced bilaterally because a decrease of input into the linear pathway on the lesioned side affects the VOR gain on both sides equally. This symmetric effect is due to the fact that, during ipsilesional head impulses, the contralesional linear path-

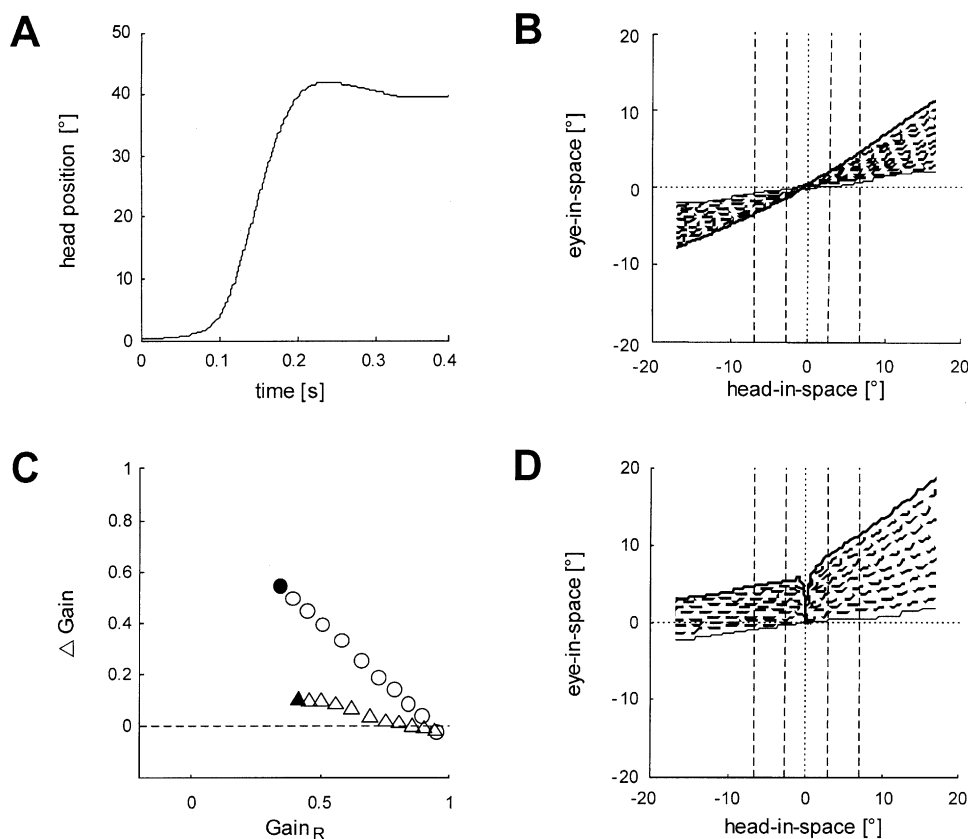


FIG. 5. Performance of the model by Lasker et al. (2000) upon an actual head impulse (applied by A.P.) as input (duration = 0.4 s; amplitude = 40°; peak velocity = 470°/s; peak acceleration = 12,000°/s²). **A.** Position trajectory of the head impulse. The small overshoot is typical. **B.** Eye-in-space vs. head-in-space in the presence of an increasing right-sided deficit. Each trace represents the VOR simulated by the model in the presence of a right-sided vestibular deficit. The function of the right labyrinth was reduced in 10 steps (dashed lines) from normal (no deficit, thin solid line) to total loss (no function, thick solid line). No central elements were changed. Dashed vertical lines indicate intervals for determining the gain

(see Methods). **C.** Gain difference (Δ Gain) as a function of ipsilesional gain (Gain_R). Data points represent the gains from panels **B** (triangles) and **D** (circles). Filled symbols: gains as a result of a total unilateral deficit. **D.** Axes and lines as in **B**, but ipsilateral R (90 → 80 Hz), contralateral k_l (1 → 1.2), and contralateral k_n (0.00001 → 0.000025) were changed proportionally to the peripheral vestibular deficit. Note that the spontaneous nystagmus manifests itself indirectly by eye-in-space displacements to the right evoked by the slightest head-in-space movement to either side, although it cannot be seen directly in this plot.

way is not driven into inhibitory cutoff. The computed small asymmetry between the bilaterally reduced VOR gains (gain lower during ipsilesional head rotation) is caused solely by the nonlinear pathway on the contralesional side, which is driven into inhibitory cutoff during ipsilesional head rotation but contributes to the gain during contralesional head rotation. Note that, in the absence of central changes, the impact of the contralesional nonlinear pathway on the VOR gain during contralesional head impulses is small. When central changes are permitted by changing ipsilesional R (90 → 80 Hz), contralesional k_l (1 → 1.2), and contralesional k_n (0.00001 → 0.000025) proportionally to the peripheral deficit (Fig. 5D), the model increases the VOR gain for contralesional head impulses and generates spontaneous nystagmus.

Plotting ipsilateral gain versus the difference between ipsi- and contralesional gain demonstrates the

increase of gain difference as a function of the growing ipsilesional deficit (Fig. 5C). When ipsilesional R , contralesional k_l , and contralesional k_n remain unchanged, the increasing unilateral deficit has a small effect on gain asymmetry (triangle in Fig. 5C derived from Fig. 5B). In the presence of a total unilateral deficit, the gain difference amounts only approximately 0.1 (filled triangle). With simultaneous changes of all three variables, however, the asymmetry increases strongly as a function of the ipsilesional deficit (circles in Fig. 5C derived from Fig. 5D). A total unilateral deficit leads to a gain difference of about 0.55 (filled circle). Of course, with these simulations we do not suggest that central changes are in fact proportional to the unilateral peripheral vestibular deficit in individual patients. Other factors, such as time elapsed after the lesion, head movement activity, and age, will also play a role.

Figure 6 compares the data of the patients with the prediction of the model. Again, gain differences are plotted as a function of the ipsilesional gain (compare with Fig. 5C). Based on the simulations, we identified an area that includes all possible output values resulting from variations of the unilateral peripheral deficit (0%–100%) and of the parameters of central changes (ipsilesional R and contralesional k_i , k_n) proportional to the deficit. The data points of the patients showed a wide distribution: 61% were located inside the area that could be predicted by the model. The slope of the regression through all data points amounted to 0.76 and was approximately in between the simulations with (line a) and without (line b) changing ipsilesional R , contralesional k_i , and contralesional k_n . Recall that the parameters of the model are derived from data obtained in experimental animals. Despite this caveat, the close approximation of the computer simulation with the majority of VN patients, in whom a purely unilateral deficit is suspected, is noteworthy.

DISCUSSION

Our study demonstrates that the asymmetry of the vestibulo-ocular reflex (VOR) evoked by horizontal head impulses decreases over time in patients after clinically suspected vestibular neuritis (VN). This improvement is due mainly to a gain increase for head impulses toward the ipsilesional side and takes place primarily within the first few weeks after the onset. Our results are in contrast to the findings in patients after unilateral neurectomy, in whom the gain asymmetry remained unchanged over time (Halmagyi et al. 1990). The same lack of improvement of the horizontal high-acceleration VOR was also observed in guinea pigs with complete unilateral vestibular loss (Vibert et al. 1993; Gilchrist et al. 1998). Thus, it is fair to assume that the observed ipsilesional VOR gain recovery is a result of spared peripheral vestibular function on this side. Whether the ipsilesional gain increase is a result of incremental recovery of peripheral vestibular function or whether unchanged residual peripheral input drives an emerging central compensation mechanism cannot be inferred from our results.

How does the gain for the contralesional head impulse relate to the ipsilesional deficit? To answer this question, we need to consider the physiology of central vestibulo-ocular pathways. The model developed by Lasker et al. (2000) on the bases of experimental results in squirrel monkeys (see Fig. 4) makes an interesting prediction for unilateral peripheral vestibular deficits: Without central adaptation leading to internal gain increases of the contralesional linear and non-

linear pathways and a decrease of the resting rate of the ipsilesional central vestibular neurons, the gain for contralesional head impulses declines much more than was observed in the majority of our patients and in the patients after unilateral vestibular neurectomy reported by others (Halmagyi et al. 1990; Aw et al. 1996, 2001). According to the model by Lasker et al., a total unilateral vestibular deficit results, without adjustments of the central internal gains and the resting rate, in an ipsilesional VOR gain of ~ 0.4 and a contralesional VOR gain of ~ 0.5 (filled triangle in Fig. 5C). On the other hand, effective adaptive changes of the central internal gains and the resting rate lead to an ipsilesional VOR gain of ~ 0.3 and a contralesional VOR gain of ~ 0.9 (filled circle in Fig. 5C).

The output of the model by Lasker et al. (2000) can be qualitatively explained by considering the symmetric and asymmetric properties of central vestibular pathways. The linear pathways contribute equally during ipsilateral and contralateral rotations, even during high accelerations. In other words, a unilateral deficit of the linear pathways leads to the same gain reduction on both sides. In the presence of a unilateral vestibular deficit, the higher gain on the contralesional side is a result of the adapted contralesional nonlinear pathway that enhances the VOR mainly during contralesional head impulses. Recall that during ipsilateral head impulses, the contralesional nonlinear pathway is driven into inhibitory cutoff. In the absence of central changes, the intact contralesional nonlinear pathway contributes little to the contralesional gain. With the central changes implemented in the model, however, the contribution of the adapted nonlinear pathway becomes large.

Ewald's second law states that excitation drives the vestibulo-ocular reflex better than inhibition (Ewald 1892). In the model of Lasker et al., Ewald's second law is implemented by the nonlinear pathway that is driven mainly by excitatory semicircular canal input. While in healthy subjects the impact of the nonlinear pathway, and hence Ewald's second law, is small, the situation is different after a unilateral decrease of peripheral vestibular function. In this case, the model assumes central adaptive changes of the nonlinear pathway to keep the contralesional VOR gain close to normal, i.e., Ewald's second law becomes more powerful.

According to the model, the more effective central compensation is, the closer the contralesional gains move up to the normal range. For that reason, assuming one applies the model by Lasker et al., the relatively small reduction of contralesional gains, as observed in the majority of our patients, can be explained only by central "upregulation". In the model this is achieved by increasing the gains of contralesional linear and nonlinear vestibulo-ocular pathways. Based on these considerations, a small contralesional

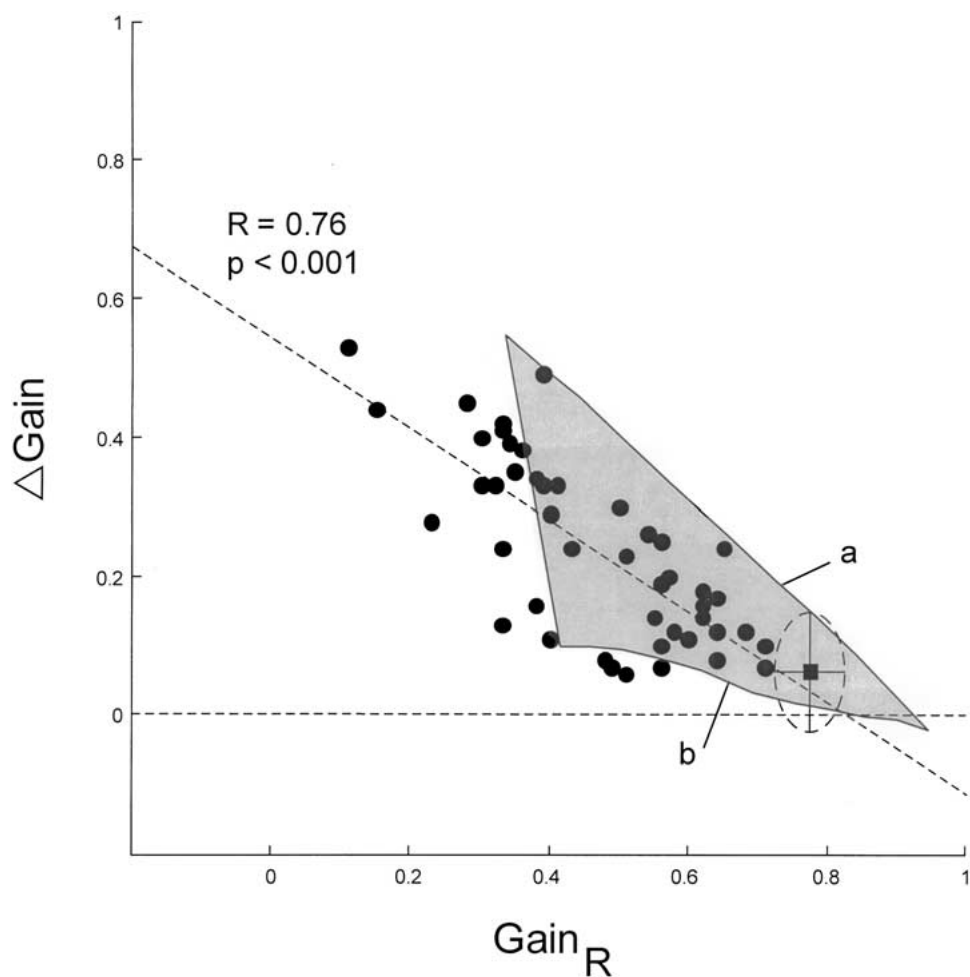


FIG. 6. Comparison of patients' data with that from the model by Lasker et al. (2000) Δ Gain: differences between gains; Gain_R : gains during head impulses toward the right side, which was always the weaker side. Filled circles: individual testing sessions ($N = 47$ in 37 patients); filled square: average data point from healthy subjects (ellipse with horizontal and vertical radii: ± 1 SD); horizontal dashed

line: Δ Gain = 0; oblique dashed line: linear regression through data cloud. Gray area: all possible output values of the model when one varies the unilateral peripheral deficit (0–100) and gradually changes the central elements in proportion to the deficit (see Fig. 4). Line a: full changes of central elements (corresponding to Fig. 5D). Line b: no changes of central elements (corresponding to Fig. 5B).

gain reduction of high-acceleration VOR in a unilateral peripheral deficit should not be interpreted as central “downregulation” that the brain imposes to decrease the asymmetry of the horizontal VOR (Fetter and Zee 1988). A small asymmetry, rather, speaks for a deficient central “upregulation” of the contralesional gain. Indeed, it seems that the central nervous system does not attempt to balance the horizontal VOR gains but instead tries to boost the contralesional gain to a value close to normal.

Judged by the weak correlation between ipsilesional gain and the difference of VOR gain between right and left, the effectiveness of this centrally mediated contralesional upregulation seems to vary considerably among patients with VN (Fig. 6). Moreover, patients with minimal upregulation seem to closely resemble patients with a symmetrical bilateral peripheral deficit. This makes it difficult to de-

cide in these cases whether a unilateral deficit with insufficient upregulation or a bilateral deficit is present. If gains are outside of the area explainable by a total unilateral peripheral vestibular deficit, a bilateral lesion should be considered (Fig. 6, left of the gray area). In fact, more than one third of our patients had initial gains that suggested bilateral VN, although the gains were asymmetrical. However, age-dependent parameters, which presently are not included in the model, could shift the leftmost border of the area further to the left so that the percentage of bilaterally affected patients would be lower. Also, we point out that the computer simulations relied on the assumption that the primary afferents of linear and nonlinear pathways are equally affected by VN. Finally, we reemphasize the caveat that the parameters of the model are based on experiments in squirrel monkeys.

Of course, we were not able to separate unilateral from bilateral cases *in vivo*. However, postmortem findings in unselected human preparations of bilateral infections of the labyrinth or the vestibular ganglion by herpes simplex virus type 1 in the majority of cases (Arbusow et al. 2001), supports the hypothesis that at least some of our patients after VN were affected bilaterally. Future studies should try to correlate data from vestibular testing with data from methods that allow quantifying inflammations of the vestibular nerve and labyrinth on both sides, e.g., by MRI (Karlberg et al. 2004).

In conclusion, we have demonstrated that, after vestibular neuritis, the asymmetry of horizontal gain of high-acceleration VOR decreases during the first few weeks due to an ipsilesional gain increase. We conjecture that the main source of the gain asymmetry is due to a central upregulation of the contralesional gain, which is already present during the first measurements after the onset of the vestibular neuritis. In addition, we have provided indirect evidence that a number of patients, after a sudden peripheral vestibular asymmetry, may suffer from asymmetrical bilateral vestibular neuritis.

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Head-Shaking Nystagmus Depends on Gravity

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ABSTRACT

In acute unilateral peripheral vestibular deficit, horizontal spontaneous nystagmus (SN) increases when patients lie on their affected ear. This phenomenon indicates an ipsilesional reduction of otolith function that normally suppresses asymmetric semicircular canal signals. We asked whether head-shaking nystagmus (HSN) in patients with chronic unilateral vestibular deficit following vestibular neuritis is influenced by gravity in the same way as SN in acute patients. Using a three-dimensional (3-D) turntable, patients ($N = 7$) were placed in different whole-body positions along the roll plane and oscillated (1 Hz, $\pm 10^\circ$) about their head-fixed vertical axis. Eye movements were recorded with 3-D magnetic search coils. HSN was modulated by gravity: When patients lay on their affected ear, slow-phase eye velocity significantly increased upon head shaking and consisted of a horizontal drift toward the affected ear (average: $1.2^\circ/\text{s} \pm 0.5 \text{ SD}$), which was added to the gravity-independent and directionally nonspecific SN. In conclusion, HSN in patients with chronic unilateral peripheral vestibular deficit is best elicited when they are lying on their affected ear. This suggests a gravity-dependent mechanism similar to the one observed for SN in acute patients, i.e., an asymmetric suppression of vestibular nystagmus by the unilaterally impaired otolith organs.

Keywords: nystagmus, neurootology, vestibular neuritis, otoliths, body tilt

INTRODUCTION

A sudden unilateral peripheral vestibular deficit leads to an asymmetry of tonic vestibular input signals and thus spontaneous eye drift toward the ipsilesional side. Patients avoid lying on their affected ear, because the affected-ear-down position intensifies the vertigo. In fact, an increase of spontaneous nystagmus (SN) is observed in this position, indicating an enhancement of the horizontal semicircular canal imbalance by the changed orientation of the gravity vector relative to the head (Fluur 1973). Such a modulation of canal-mediated SN by gravity strongly suggests an interaction between otolith and semicircular canal pathways.

In the course of vestibular compensation, the velocity of spontaneous eye drift gradually decreases. Patients with chronic unilateral vestibular deficit may yet show some SN in darkness, but not during ocular fixation in the light (Baloh and Honrubia 2001). Nystagmus can still be detected, however, after shaking the head rapidly over 20 to 30 cycles in the horizontal plane (Kamei et al. 1964) or after whole-body oscillation on a turntable about an Earth-vertical axis (Fetter et al. 1990; Katsarkas et al. 2000). This so-called head-shaking nystagmus (HSN) is considered to be a sensitive symptom for detecting asymmetries in the vestibular system (Hain et al. 1987; Fetter et al. 1990; Hain and Spindler 1993).

The presence of HSN reflects a directional imbalance of the vestibuloocular reflex (VOR) in the high-frequency range after unilateral vestibular lesions. During high-acceleration head rotations, the VOR is mainly generated by the excited side (Ewald 1892), because the nonlinear pathway of the inhibited side is driven into inhibitory cutoff (Lasker et al. 2000). For nystagmus to appear after head oscillation has

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stopped, the directionally asymmetric response must have been stored during head shaking to be discharged thereafter. Therefore to elicit HSN, the brainstem network that transiently accumulates the vestibular velocity signals, the so-called “velocity storage” (Raphan et al. 1979), must be operative to receive and perpetuate the input that predominantly comes from the healthy ear (Fetter et al. 1990; Hain and Zee 1992). Consequently, HSN generally beats toward the healthy ear. Central mechanisms under the control of the cerebellum, however, may lead to a secondary phase of nystagmus in the opposite direction or even a reversed nystagmus right from the beginning (Asawavichiangianda et al. 1999).

We asked whether the primary phase of horizontal HSN (HSNh) in patients with chronic unilateral vestibular deficit after vestibular neuritis is influenced by the orientation of the gravity vector and whether such a gravity-dependent modulation would resemble the one seen in horizontal SN (SNh) of patients with acute unilateral vestibular deficit. This would indicate that otolith-mediated mechanisms interfering with the asymmetry of semicircular canal signals are the same for both SNh and HSNh.

METHODS

Definition

The term “head-shaking nystagmus” (HSN) was applied to describe nystagmus appearing after oscillation of the head in space. This broader definition of HSN, which goes beyond head shaking on the trunk at the bedside, is in line with the existing literature and includes whole-body oscillation on a turntable (Fetter et al. 1990; Katsarkas et al. 2000).

Subjects

Three-dimensional (horizontal, vertical, torsional) eye movements before, during, and after head shaking were recorded in seven patients (four male, 28–77 years) with chronic unilateral peripheral vestibular deficit after vestibular neuritis (Schuknecht and Kitamura 1981; Arbusow et al. 2000). Another four patients also participated in the study, but opted not to complete the experimental protocol because of nausea. The diagnosis was based on the patient’s history and bedside testing. The clinical examination was performed by an experienced neurotologist (D.S.). Clinically, horizontal head-shaking nystagmus under Frenzel glasses was present in all seven patients. Quantitative head impulse testing with search coils confirmed the unilateral peripheral vestibular deficit (Aw et al. 1996). In six patients the deficit was right-

sided, in one patient left-sided. Because search-coil head impulse testing is more sensitive than caloric testing in chronic patients after vestibular neuritis (Schmid-Priscoveanu et al. 2001), caloric irrigation was not performed in all patients. The average duration since the onset of the vestibular deficit was 3.5 years (range: 3 months–10 years). The comparison group consisted of 12 healthy subjects (six male, 25–59 years).

The subjects gave their consent to participate in this study after being informed of the experimental procedures. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the Declaration of Helsinki for research involving human subjects.

Experimental set-up

Subjects were seated upright on a turntable with three servo-controlled motor-driven axes (prototype built by Acutronic, Jona, Switzerland). The head was restrained with an individually molded thermoplastic mask (Sinmed BV, Reeuwijk, The Netherlands). Subjects were positioned so that the center of the interaural line was at the intersection of the three axes of the turntable. Pillows and safety belts minimized movements of the body. The chair was pitched 20° in the nose-down direction to position the lateral semicircular canals approximately horizontal.

Eye and head movement recording

Three-dimensional (3-D) eye and head movements were recorded with dual search coils (Skalar Instruments, Delft, The Netherlands). The coil frame (side length: 0.5 m) generated three orthogonal digitally synchronized magnetic wave field signals of 80, 96, and 120 kHz. A digital signal processor computed a fast Fourier transform in real-time on the digitized search coil signal to determine the voltage induced on the coil by each magnetic field (system by Primelec, Regensdorf, Switzerland). Coil orientation could be determined with an error of less than 7% over a range of $\pm 30^\circ$ and with a noise level of less than 0.05° (root mean squared deviation).

Search coil annuli were calibrated with a method described elsewhere (Straumann et al. 1995). A dual search coil was placed around the cornea of the right eye after local anesthesia with oxybuprocaine 0.4%. A second coil for measuring head movements was fixed on the front teeth via silicon dental impression paste (Blu-Mousse® Classic, Parkell, Inc., Farmingdale, NY, USA). Eye, head, and chair position signals were digitized at 1000 Hz/channel with 16-bit resolution,

and stored on a computer hard disk for offline processing.

Experimental protocol

A chair-fixed laser dot was projected straight ahead onto a tangent screen at a distance of 0.59 m in front of the subject's eyes. Every 2 s the laser dot was turned on for a duration of 20 ms. Subjects were instructed to look at the laser dot and to keep their eyes at this position during the off periods. The short duration of on periods ensured that the smooth pursuit system was not activated.

The chair was rotated in the roll plane in 45° steps from the left ear-down to the right ear-down position (five positions: 90° and 45° left ear-down; upright; 45° and 90° right ear-down). Each position was held for a 90 s period consisting of three phases: (1) 30 s of stationary chair position; (2) 30 s of turntable oscillation about the head-fixed vertical axis (approximately orthogonal to the lateral semicircular canals; see Experimental set-up) with an amplitude of 10° and a frequency of 1 Hz; (3) 30 s of stationary chair position. Eye movements during the first interval corresponded to spontaneous nystagmus (SN), during the second interval to the vestibuloocular reflex (VOR), and during the third interval to head-shaking nystagmus (HSN). Note that oscillating the subject about the head-fixed yaw axis implied some degree of perrotatory VOR dumping, except in the upright position, in which the rotation axis was Earth-vertical (Bockisch et al. 2003).

Data analysis

Search coil signals from the right eye and the head were processed with interactive programs written in MATLAB™ Version 6. 3-D positions of eye and head were expressed as rotation vectors (Haustein 1989), and corresponding 3-D velocities as angular velocity vectors (Hepp 1990). The transverse plane of the head-fixed coordinate system was aligned with the Earth-horizontal with the head pitched 20° nose-down. In this position, defined as upright, the horizontal semicircular canals were approximately parallel to the Earth-horizontal plane. For convenience, the lengths of rotation vectors and angular velocity vectors were given in degrees and degrees per second (°/s), respectively. According to the right-hand rule, eye rotations to the left, down, and clockwise from the subject's point of view are positive. To facilitate the analysis, 3-D eye movement directions in the patient with the left-sided vestibular lesion were mirrored, as if the right ear had been affected by the vestibular neuritis. This was accomplished by multiplying the horizontal and torsional eye and head movement components by (-1) . Thus in the analysis of this patient's data, it was as if the right side was the affected side.

In each turntable position, eye movements during intervals 10 s before and 10 s after head shaking were analyzed by interactively selecting sections of slow-phase eye movements between quick phases of nystagmus. To determine the dynamics of the ocular response during whole-body oscillation, eye velocity was desaccaded by overlaying all cycles and comput-

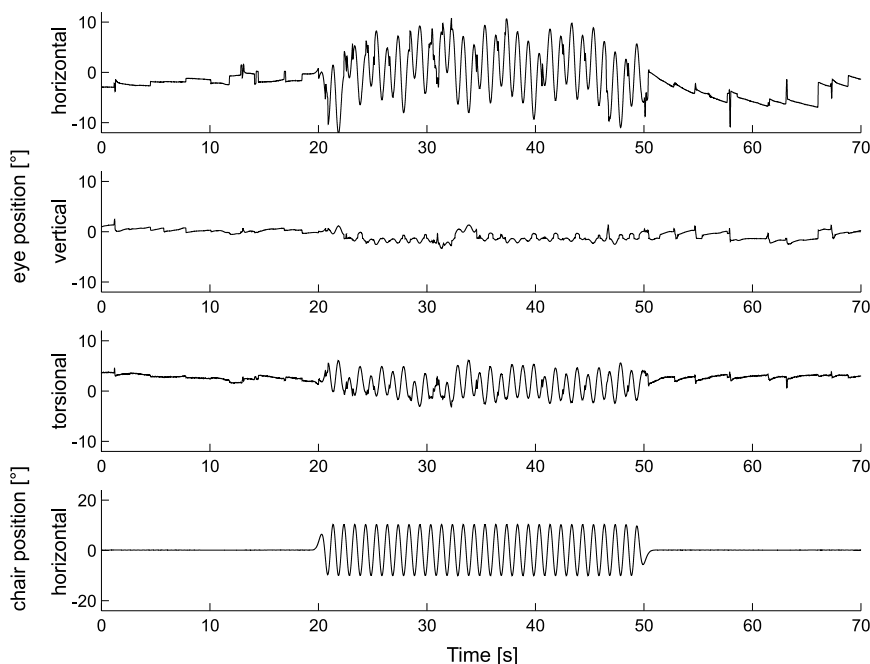


FIG. 1. Three-dimensional position traces (upper three panels: horizontal, vertical, torsional) of the right eye in an upright sitting patient (P.I.) with a right-sided peripheral vestibular deficit. Eye movements to the left, down, and clockwise, as seen by the subject, are positive according to the right-hand rule. Chair position (lowest panel) oscillated in the horizontal direction only (1 Hz, $\pm 10^\circ$). Traces are clipped 20 s before and 20 s after the turntable oscillation.

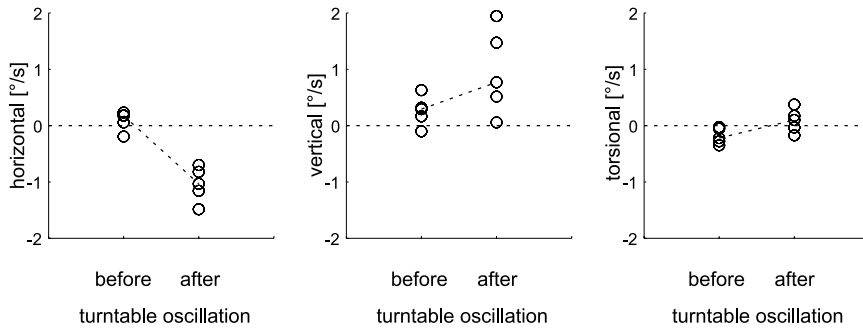


FIG. 2. Average velocities of individual slow phases (open circles) of nystagmus before and after horizontal turntable oscillation in the same upright sitting patient as in Figure 1. Eye movement directions according to the right-hand rule. Selected slow phases were within 10 s before and after turntable oscillation. Dashed lines connect averages of data points before and after turntable oscillation.

ing the median eye response (Schmid-Priscoveanu et al. 2000). Then, horizontal eye velocity was plotted against horizontal chair velocity. The slope of the first-linear regression yielded the gain, its offset the velocity bias.

RESULTS

Figure 1 shows three-dimensional (3-D) eye position traces measured in an upright-positioned patient with a right-sided peripheral vestibular deficit. Before turntable oscillation, only a small drift was noted. After oscillation, horizontal drift, directed toward the affected right side, increased considerably more than vertical and torsional drifts. Hence the resulting “head-shaking nystagmus” was mainly horizontal.

For the same example, average velocities of nystagmus slow phases before and after turntable oscillation are depicted in Figure 2. The largest change of slow-phase eye velocity (averages connected by dashed lines) occurred in the horizontal eye movement plane: before head shaking, velocities scattered around zero; after head shaking, the eyes drifted toward the right side, i.e., the side of the vestibular lesion (unpaired t -test: $p < 0.01$). Downward-directed vertical drift

increased slightly after head shaking, but data points scattered widely ($p = 0.09$). Torsional drift was directed counterclockwise before head shaking, but reversed its direction after head shaking ($p = 0.04$).

Figure 3 shows average horizontal eye velocities before (circles) and after head shaking (stars) in different whole-body positions along the roll plane in a healthy subject (Fig. 3A) and in the same patient as in the previous example (Fig. 3B). In the healthy subject, the horizontal velocity of spontaneous drift and drift after head shaking scattered around zero independent of body position. In the patient, the horizontal spontaneous drift did not modulate with gravity. Horizontal drift velocity after head shaking, however, showed a clear gravity-dependent gradient with an increasing rightward drift from 90° left ear-down to 90° right ear-down. Accordingly, slow-phase eye velocity toward the affected right side was most prominent when the patient was lying on the affected right ear.

Figure 4 depicts slow-phase eye velocity of all patients in left ear-down, upright, and right ear-down whole-body positions before and after head shaking. For comparison, the differences of drift velocities between the same conditions in healthy subjects are also plotted. Recall that in all patients the right side corresponds to the affected side, i.e., eye movement

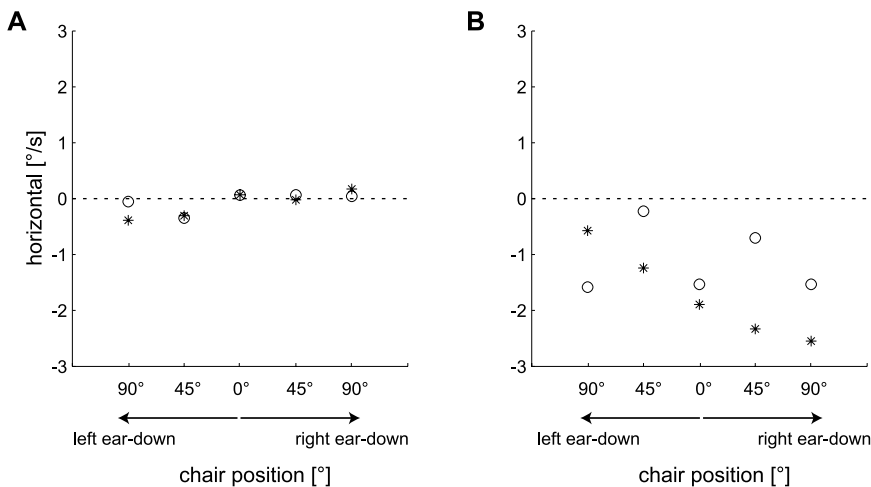


FIG. 3. Examples of average horizontal slow-phase eye velocities before (circles) and after (stars) horizontal turntable oscillation in different body positions along the roll plane. Eye velocity to the left is positive. **A** Healthy subject (A.P.). **B** Same patient as in Figures 1 and 2. Note the increase of horizontal eye velocity toward the affected right side after oscillation when the patient is rolled toward the affected right ear.

data in the only one patient with a left-sided lesion were mirrored (see Methods). Horizontal slow-phase eye velocity in the upright and nonaffected (=left) ear-down positions was not significantly different from zero before (open circles; triangle \equiv mirrored data point) and after (stars; triangle \equiv mirrored data point) head

shaking (ANOVA: $p_{\text{horizontal}} = 0.94$). In the affected (= right) ear-down position, however, head shaking elicited a significant (paired t -test: $p < 0.01$) change of horizontal slow-phase eye velocity toward the undermost ear (average increase of slow-phase eye velocity by head shaking: $1.2^\circ/\text{s} \pm 0.5 \text{ SD}$). There was no

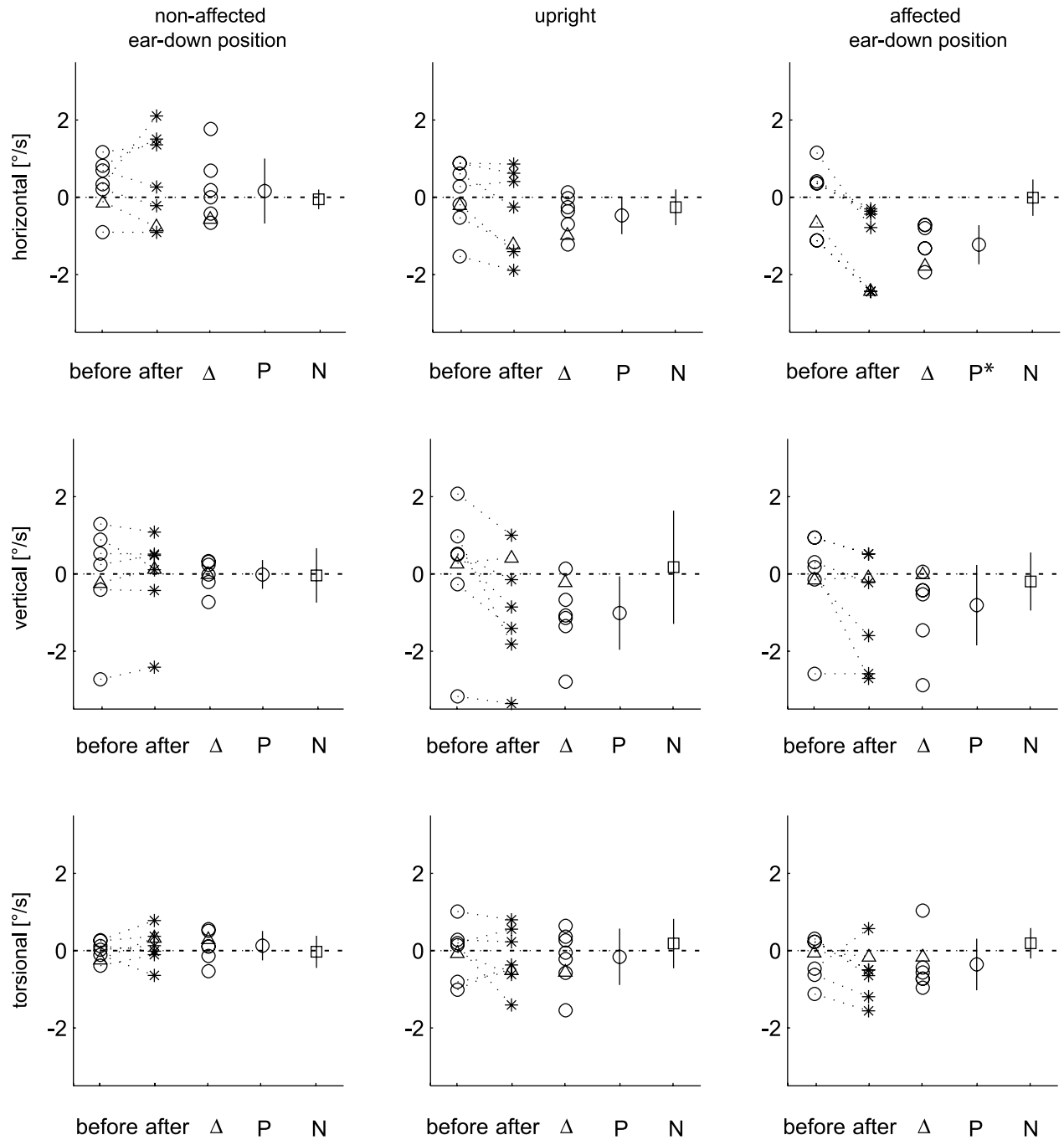


FIG. 4. Comparisons between average slow-phase eye velocities before (open circles) and after (stars) horizontal turntable oscillation in all patients in the non-affected ear-down, upright, and affected ear-down positions. Eye movement directions according to right-hand rule. In the ear-down positions, each data point on one side corresponds to the average eye velocity measured in the 90° and 45°

body positions. In the one patient with a left-sided deficit (data depicted as triangles), eye movement directions were mirrored, thus, for analysis, the right ear was always the affected ear. Dotted lines connect eye velocities of individual patients. Δ : Difference between slow-phase eye velocities before and after oscillation. P: Average $\Delta (\pm 1 \text{ SD})$ in patients. N: Average $\Delta (\pm 1 \text{ SD})$ in healthy subjects.

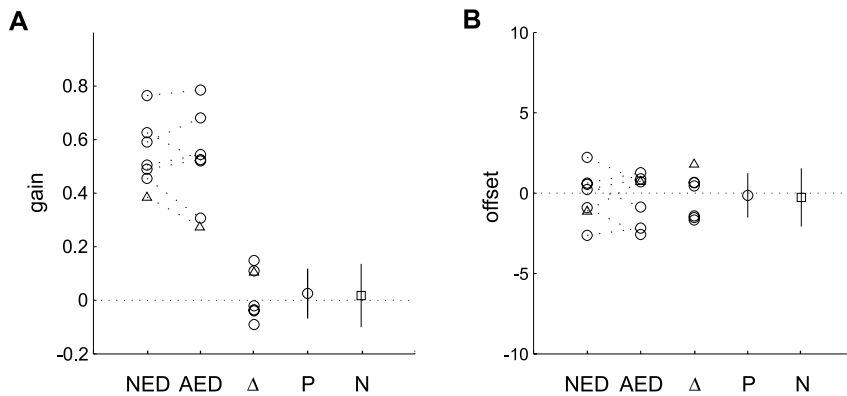


FIG. 5. Parameters of sine fits through desaccaded horizontal slow-phase velocity during horizontal turntable oscillation. Comparison between averages of individual patients (open circles; triangle for mirrored data in the one patient with a left-sided deficit) in affected ear-down (AED) and non-affected ear-down (NED) roll body positions. Δ : Differences, P: Average $\Delta (\pm 1$ SD), N: Average $\Delta (\pm 1$ SD) in healthy subjects. **A** Gain. **B** Offset.

significant effect of horizontal head shaking on slow-phase velocity in the vertical and torsional directions (ANOVA: $p_{\text{torsional}} = 0.76$; $p_{\text{vertical}} = 0.79$). In the healthy subjects, no significant differences between drift velocities before and after head shaking (open squares with error bars) were observed in any roll body position tested.

We asked whether the influence of gravity on ocular responses was not only apparent after, but also during head shaking. Figure 5A shows average gain values of the horizontal vestibuloocular reflex elicited by horizontal turntable oscillation in the non-affected ear-down and the affected ear-down positions. In all patients, no significant differences were noted between the gains in these roll body positions. As depicted in Figure 5B, the average offset of the fitted sine to horizontal ocular velocity during horizontal turntable oscillation was not different from zero in both side positions.

DISCUSSION

This study analyzed the influence of gravity on three-dimensional (horizontal, vertical, and torsional) slow-phase eye velocity before and after horizontal head shaking in patients with chronic unilateral peripheral vestibular deficit after vestibular neuritis. Head shaking was applied by whole-body oscillation about a head-vertical axis that was oriented approximately perpendicular to the lateral semicircular canals. We emphasize that this type of head shaking does not exactly represent the head shaking used at the bedside. However, the aim of our study was to apply the head shaking stimulus in a reproducible way in different head roll orientations, which could not be carried out if the head oscillation were performed by hand.

In all roll positions, including upright, patients showed horizontal eye drift both before (=horizontal spontaneous nystagmus, SNh) and after (=horizontal

head-shaking nystagmus, HSNh) head shaking. Slow-phase eye velocity of SNh scattered around zero and the direction of nystagmus was independent of the side of the vestibular deficit. In fact, average slow-phase eye velocity among the seven patients was not influenced by gravity (=no positional nystagmus) and was not significantly different from zero in all body positions, which was most likely the result of vestibular compensation.

When horizontal head shaking was applied to patients in the upright position, slow-phase eye velocity did not significantly change from SNh. This result is in agreement with the finding of Katsarkas et al. (2000) that, in patients with unilateral peripheral vestibular loss, no consistent velocity bias toward the lesioned side for peak velocities of oscillatory head shaking $<160^\circ/\text{s}$ was elicited. However, when head shaking was applied to patients lying on their affected ear, we found a significant horizontal velocity bias toward this side. Together with the observation of unaffected horizontal slow-phase eye velocity by head shaking when patients were lying on their healthy ear, we can conclude that the head tilt toward the affected side had a facilitating effect (Fig. 4). Because of the dynamic restrictions of our turntable, the peak velocity was lower than with manual head shaking. This probably explains why turntable oscillation did not elicit HSNh in the majority of upright-seated patients, even when HSNh in the same patients was visible under the Frenzel glasses after manual head shaking in upright position. In addition, we cannot exclude that this difference between turntable and manual head shaking might be attributable to the lack of proprioceptive neck signals during the whole-body oscillation. In fact, the cervicocolic reflex is known to increase its gain in patients with vestibular deficits (Heimbrand et al. 1996). Nevertheless, our study demonstrates that a significant portion of head-shaking nystagmus depends on vestibular stimulation.

The gravity dependence of HSNh in our chronic patients is comparable to the gravity dependence of

SNh in acute patients, in whom horizontal slow-phase eye velocity increases when they lie on the affected ear. This indicates an interaction between otolith and semicircular canal signals. The exact nature of this interaction is still uncertain. Fluor's hypothesis on the gravity dependence of SNh in acute patients is based on the presumption that otolith signals are used by the central nervous system to reduce the imbalance between semicircular canal signals (Fluor 1973). Because otolith signals are directionally polarized, i.e., mainly responding to ipsilateral head roll (Fernandez and Goldberg 1976), such an otolith-mediated suppression of vestibular nystagmus is weaker when the head is rolled toward the affected ear, provided the otolith organs or otolith afferents are impaired on this side as well. It is indeed likely that the utricle has been at least partially afflicted in our patients, because of the predominant involvement of the superior division of the vestibular nerve in vestibular neuritis (Fetter and Dichgans 1996). As slow-phase eye velocities of both SNh and HSNh increase when patients are positioned with the affected ear down, we conjecture that the mechanisms of gravity dependence for SNh and HSNh are similar, i.e., the otolith-mediated suppression of asymmetric tonic semicircular canal signals is more effective when patients are lying on the ear that provides normal otolith signals to the central nervous system.

We can only speculate at what level the modulation of HSNh takes place. Because the gain of the vestibuloocular reflex during head shaking did not differ between different body positions along the roll plane, the gravity dependence of HSNh cannot be explained by a head-position-dependent variation of vestibular input into velocity storage. Rather, otolith signals seem to influence the velocity storage mechanism itself, most likely by shortening the time constant (=dumping mechanism) via the vestibulo-cerebellum, specifically the nodulus (Hain et al. 1988). In fact, our results suggest that the gravity dependence of HSNh, and perhaps also of SNh, represent an asymmetry of the cerebellar "dumping" mechanism as a result of a unilateral otolith deficit.

An alternative explanation of SNh and HSNh is based on the gravito-inertial force (GIF) resolution hypothesis by Merfeld and colleagues on how the brain solves the tilt-translation dilemma (Merfeld et al. 1993; Merfeld and Young 1995). These authors propose an internal representation of gravity by the central nervous system. Any difference occurring between the GIF vector sensed by the otoliths and the internal gravity vector is interpreted as a vector of linear translation. Extending the GIF resolution hypothesis to patients with unilateral peripheral vestibular hypofunction, the observed gravity dependence of SNh and HSNh can be predicted as follows:

If patients receive less otolith input when lying on the affected ear, the difference between the GIF vector and the internal vector (i.e., the estimated head-horizontal translation in the direction of the uppermost ear) is larger, which leads to an increase of the horizontal slow-phase eye velocity (SNh in acute patients, HSNh in chronic patients) toward the undermost ear.

As suggested by earlier experiments on static and dynamic otolith-ocular reflexes in the roll plane in the presence of unilateral peripheral vestibular hypofunction, there is a central compensation of the unilateral utricular deficit (Schmid-Priscoveanu et al. 1999). This would explain our finding that, in the chronic state of a unilateral vestibular deficit, SNh was not significantly different between the two ear-down positions. However, the gravity dependence of HSNh in our chronic patients clearly indicates that the central compensation of the utricular asymmetry is incomplete, i.e., can be unmasked by dynamic semicircular canal stimulation, if the canal signals are asymmetrically impaired.

In conclusion, we have shown a clear modulation of HSNh by gravity in patients with chronic unilateral peripheral vestibular deficit due to vestibular neuritis. The increase in horizontal slow-phase velocity of HSNh, which appeared when patients were lying on the affected ear, was the result of a head-shaking-induced drift added to SNh. Thus the most efficient body position to elicit HSNh, and therefore to unmask the unilateral involvement of otolith organs or their afferents, is the roll position with the affected ear down. In this position HSNh may be present, even if central compensation has already abolished the gravity dependence of SNh.

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Vestibular neuritis: Vertigo and the high-acceleration vestibulo-ocular reflex

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■ **Abstract** Patients after vestibular neuritis (VN) often report persistent dizziness and disequilibrium. We correlated persistent symptoms with sustained impairment of the high-acceleration horizontal vestibulo-ocular reflex as determined by quantitative search-coil head-impulse testing (qHIT). In 47 patients, qHIT was recorded

0–60 months and symptoms assessed with the Yardley Vertigo Symptom Scale short form ≥ 18 months after VN onset. No correlation between the magnitude of high-acceleration vestibular impairment and the severity of vertigo symptoms was observed. The lack of a symptom-qHIT correlation suggests that defective compensation at a more rostral level in the central nervous system may be responsible for protracted symptoms in VN patients.

■ **Key words** head-impulse test · questionnaire · neuro-otology

Introduction

Vestibular neuritis (VN) is defined as a sudden unilateral deficit of the peripheral vestibular organ (labyrinth or nerve) without auditory symptoms in otherwise healthy subjects. Signs and symptoms result from an imbalance of the tonic discharge between the impaired and intact vestibular afferents. Recovery is due to a combination of peripheral vestibular restoration and central compensation [4]. The time course of recovery varies between individuals and, contrary to conventional clinical knowledge [3], almost 50 % of patients with VN report sustained dizziness and disequilibrium [2, 5, 6, 9, 11, 12]. Vestibular function when assessed by caloric irrigation, rotatory chair testing, posturography, or clinical balance testing does not seem to differ between patients with sustained symptoms and symptom-free patients [2, 6, 10–12]. However, a limitation of the latter studies is

that they all rely on measurements of low-frequency components of vestibular function. This is important because Schmid-Priscovescu et al. showed that the low-frequency vestibular function, as determined by caloric irrigation, becomes symmetrical, whereas the high-frequency function, assessed by quantitative search-coil head-impulse testing (qHIT), often remains impaired [14]. Since the vestibular apparatus is most efficient when transducing high-frequency components of head motion, such as occur during locomotion, it would be reasonable to expect symptoms to correlate with the qHIT. We therefore set out to compare sustained residual vestibular symptoms, as assessed by the shortened version of the Yardley Vertigo Symptom Scale (sVSS), with qHIT in VN patients.

Methods

Subjects

Forty-seven patients (27 male, 33 – 87 y [49 ± 15]) diagnosed with unilateral peripheral vestibular hypofunction due to VN participated in the study. All patients had developed acute vertigo without additional auditory or neurological symptoms and displayed spontaneous horizontal-torsional nystagmus and a pathological unilateral bedside head-impulse test during clinical examination. Patients were divided into two groups depending on the time interval between VN onset and the date of qHIT (acute: 1 day – 4 weeks, N = 14; chronic: > 4 weeks – 60 months, N = 33). The acute/chronic cutoff point was based on a previous study showing that the vast majority of improvement in qHIT takes place within 4 weeks after VN onset [13]. Twelve acute patients were tested twice at different times after VN onset; the first qHIT measurement was within the first 4 weeks after VN onset in all 12 patients and the subsequent measurement was after 4 weeks (first qHIT: 1.3 SD 1.5 weeks; subsequent: 13 SD 19 months). The comparison group for qHIT data comprised 28 healthy subjects (13 male, 18–75 y). Informed consent was obtained from all participants and the protocol was approved by the local ethics committee, in accordance with the 1964 Declaration of Helsinki.

quantitative head-impulse test (qHIT)

Three-dimensional eye and head movements were recorded in a magnetic frame (Remmel type system, modified by A. Lasker, Baltimore, MA, USA) using dual search-coils. The search-coils were calibrated before each session (see Straumann et al. [15] for details). Horizontal head impulses (amplitude: 20–40°; duration: 150–200 ms; peak velocity: ~300 °/s; peak acceleration: ~10000 °/s²) were applied by an investigator standing behind the subject who was visually fixing upon a target light 1.24 m straight ahead. The direction of the head impulses

was pseudorandomized and four to six impulses were performed in each direction. The gain of the horizontal vestibulo-ocular reflex (VOR) was determined by computing the coefficient ‘eye-in-space displacement divided by head-in-space displacement’ as head-in-space moved from 3° to 7° eccentricity from straight-ahead. We used this analysis to minimize any possible effect of latency on gain, since it is not known whether VN affects only the gain or, in addition, also the latency of the VOR. An increased latency, however, would lead to a false reduction of gain if determined at peak head velocity [13].

Gain asymmetry ($gVOR_{asym}$) in percent was computed by:

$$gVOR_{asym} = \frac{gVOR_{contra} - gVOR_{ipsi}}{gVOR_{contra} + gVOR_{ipsi}}$$

whereby $gVOR_{ipsi}$ denotes the VOR gain during head impulses to the ipsilesional side and $gVOR_{contra}$ the VOR gain during head impulses to the other side.

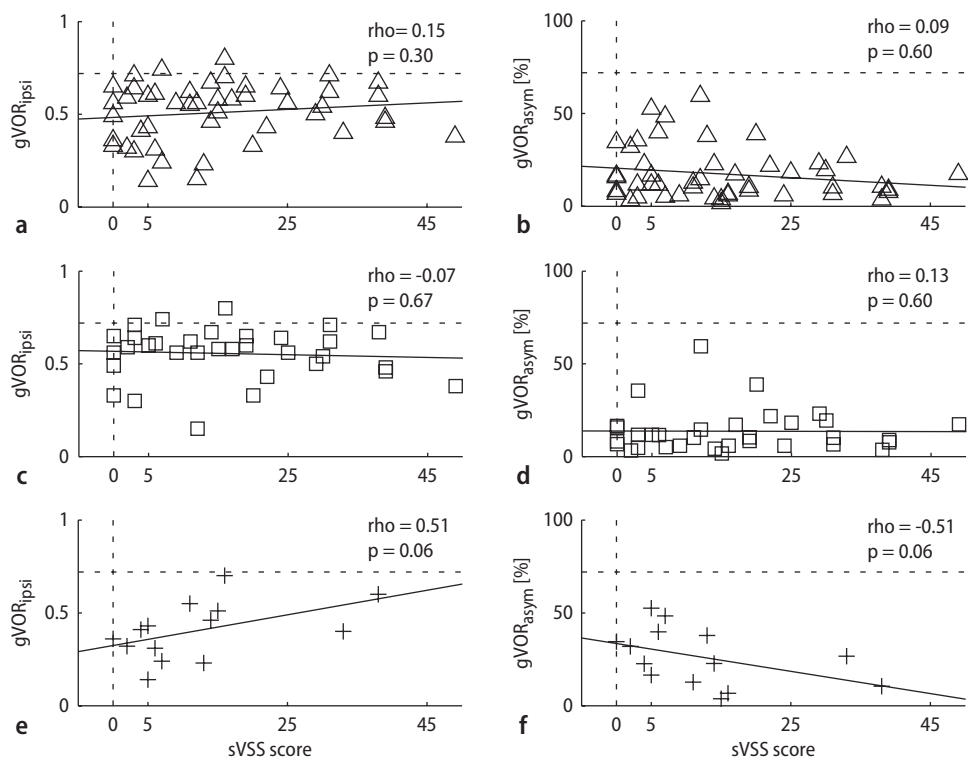
Vertigo symptom scale

Two to 98 months (46 SD 27) after vestibular examination, patients were asked to complete the shortened version of the Yardley Vertigo Symptom Scale (sVSS), measuring the frequency of dizziness, vertigo, imbalance, and related autonomic symptoms during the past 12 months [19–21].

Results

Fig. 1 plots gains of the horizontal VOR for qHIT towards the ipsilesional side (Fig. 1, left) and gain asymmetry between the contra- and ipsilesional side (Fig. 1, right) as a

Fig. 1 Horizontal VOR gains during qHIT towards the ipsilesional side (left diagrams) and gain asymmetry (right diagrams) plotted as a function of sVSS scores. Triangles (a, b): all patients (N = 47); squares (c, d): chronic patients (N = 33); crosses (e, f): acute patients (N = 14). $gVOR_{ipsi}$: VOR gains for ipsilesional qHIT; $gVOR_{asym}$: percentage of gain asymmetry between contra- and ipsilesional VOR gains (see Methods for definition). Horizontal dashed lines: lower limit of average VOR gains for healthy subjects – 2SD; vertical dashed lines: zero sVSS score corresponding to complete symptom absence. Diagonal solid lines: linear regression slopes optimized by linear squares estimation; the corresponding statistics (rho and p) indicate the strength of the relationship between the two variables obtained with nonparametric Spearman statistics. Post hoc statistical power analyses for linear regressions with one predictor revealed adequate samples sizes for acute and chronic patient groups (power > 0.80)



function of sVSS in all patients (Fig. 1 A, B) as well as in the chronic (Fig. 1 C, D) and acute (Fig. 1 E, F) groups. Age was not significantly different between symptom-free and symptomatic patients (unpaired t-test: $p = 0.6$). Neither in all patients (Fig. 1 A, B) nor in the chronic patient group (Fig. 1 C, D) did ipsilesional qHIT gains or gain asymmetries correlate with sVSS scores (Spearman rank correlation coefficients ranging between -0.07 to 0.15 , p -values > 0.1). In acute patients, contrary to what may be expected, low ipsilesional qHIT gains (Fig. 1 E) and large gain asymmetries (Fig. 1 F) tended to relate to low sVSS scores (i.e., less vertigo), but the correlation was not significant (gVOR_{ipsi}: Spearman rank correlation = 0.51 , $p = 0.06$; gVOR_{asym}: Spearman rank correlation = -0.51 , $p = 0.06$).

Fig. 2 shows ipsilesional qHIT gains (A) and corresponding gain differences between the two assessments (B) plotted as a function of sVSS scores in the 12 patients who were tested twice after VN onset. The interval between the first (Fig. 2 A, circle) and the subsequent (Fig. 2 A, cross) measurement ranged between 1 and 60 months (13 SD 19 months). Low sVSS scores appeared to correlate with large ipsilesional gain improvement (Fig. 2 B), although this correlation was not significant (Spearman rank correlation = -0.3 , $p = 0.3$).

Discussion

Our study demonstrates that persistent dizziness after VN is not significantly associated with sustained vestibular impairment as assessed by the quantitative search-coil head impulse testing (qHIT). More specifically, severe vestibular deficit in the chronic patient group did not imply a high score on the shortened version of the Vertigo Symptom Scale (sVSS), assessing dizziness, vertigo and imbalance during the past 12 months. Although a lack of congruency between persistent symptoms and vestibular function tests has been de-

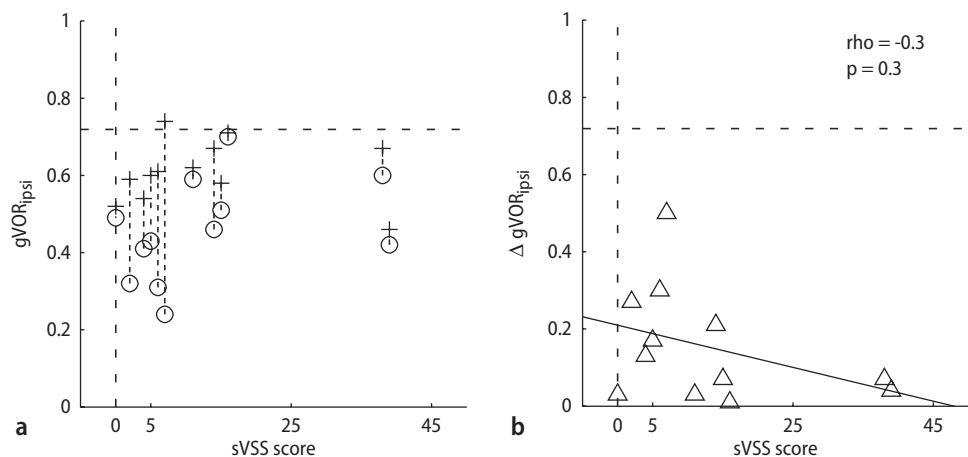
scribed previously in patients with VN [2, 5, 10–12], this is the first study showing that this conclusion also holds for the high-frequency components of vestibular function.

The fact that sVSS assessment in our study was conducted on average about 4 years after vestibular examination could be viewed as a limitation of this study. However, our explicit aim was to ascertain the presence of protracted symptoms in VN patients. We do not expect that this time interval had a major impact on the correlation of vestibular function in chronic VN patients, since qHIT measurements were also obtained when peripheral recovery and/or central compensation were stabilized [13]. Furthermore, the lack of correlation between persistent symptoms and high-frequency VOR function is unlikely to depend on sample size, as revealed by post hoc statistical power analysis (see legend Fig. 1).

A potentially interesting observation was that the two patients with very high sVSS scores showed a combination of only mild to moderate ipsilesional gain impairment and scarce gain improvement over time (Fig. 2). This finding, which might suggest a greater risk to develop chronic vertigo if gain impairment or improvement are less pronounced, needs to be verified in more patients. Such an analysis is particularly important in the light of recent suggestions that steroid treatment for acute VN improves peripheral-vestibular recovery (albeit measured with the caloric test and without symptom assessment) [1, 16].

What could be the main determinants of the long-term clinical recovery after acute VN given that residual symptoms are not correlated to conventional vestibular function tests (i.e., caloric or qHIT)? First, persistent otolith imbalance could account for sustained vestibular symptoms. To our knowledge, the only study assessing utricular function (typically affected in VN) and vestibular symptoms did not find differences in static ocular counterroll and subjective visual vertical responses

Fig. 2 Horizontal VOR gains for the first and subsequent ipsilesional qHIT measurement (a) and corresponding gain differences (b) plotted as a function of sVSS scores in patients tested twice after VN onset (N = 12). Circles: ipsilesional VOR gains (gVOR_{ipsi}) resulting from first qHIT measurement (i.e., within 4 weeks after VN onset); crosses: ipsilesional VOR gains (gVOR_{ipsi}) resulting from subsequent qHIT measurement (i.e., > 4 weeks from VN onset). Δ gVOR_{ipsi} = gVOR_{ipsi} first measurement – gVOR_{ipsi} subsequent measurement. Solid and dashed lines as in Fig. 1



between symptom-free and symptomatic VN patients [22]. Second, enhancement of the deficient VOR by early catch-up saccades, a strategy which assists gaze stabilization [18], but is not routinely assessed, may be insufficient in some patients. Recently, it has been shown that patients with a persistent abnormal bedside head-impulse test were more likely to be dizzy [22]. Possibly, in these patients, catch-up saccades do not occur during (covert saccades), but after the head impulse (overt saccades), which is easier to detect at the bedside [23]. Finally, deficient cortical adaptation, including psychophysical and psychological processes, could be responsible for protracted symptoms in VN patients [6–8, 17]. Longitudinal assessments of such central processes in VN patients, however, remain the purpose of further investigations.

Disclosure

The authors have reported no conflicts of interest.

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Accuracy of the bedside head impulse test in detecting vestibular hypofunction

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PAPER

Accuracy of the bedside head impulse test in detecting vestibular hypofunction

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Table E1 and introductory video clip.mpg can be viewed on the *J Neurol Neurosurg Psychiatry* website at <http://www.jnnp.com/supplemental>

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Objective: To determine the accuracy of the bedside head impulse test (bHIT) by direct comparison with results from the quantitative head impulse test (qHIT) in the same subjects, and to investigate whether bHIT sensitivity and specificity changes with neuro-otological training.

Methods: Video clips of horizontal bHIT to both sides were produced in patients with unilateral and bilateral peripheral vestibular deficits (n = 15) and in healthy subjects (n = 9). For qHIT, eye and head movements were recorded with scleral search coils on the right eye and the forehead. Clinicians (neurologists or otolaryngologists) with at least 6 months of neuro-otological training ("experts": n = 12) or without this training ("non-experts": n = 45) assessed video clips for ocular motor signs of vestibular deficits on either side or of normal vestibular function.

Results: On average, bHIT sensitivity was significantly (t test: $p < 0.05$) lower for experts than for non-experts (63% vs 72%), while bHIT specificity was significantly higher for experts than non-experts (78% vs 64%). This outcome was a consequence of the experts' tendency to accept bHIT with corresponding borderline qHIT values as still being normal. Fitted curves revealed that at the lower normal limit of qHIT, 20% of bHIT were rated as deficient by the experts and 37% by the non-experts.

Conclusions: When qHIT is used as a reference, bHIT sensitivity is adequate and therefore clinically useful in the hands of both neuro-otological experts and non-experts. We advise performing quantitative head impulse testing with search coils or high speed video methods when bHIT is not conclusive.

The Halmagyi–Curthoys head impulse test is, at present, the only bedside examination that allows identification of the side of a unilateral hypofunction of the peripheral vestibular system.¹ Head impulses are rapid, passive, unpredictable rotations of the head relative to the trunk. The patient is asked to fix upon a target straight ahead, usually the nose of the examiner, while the examiner turns the patient's head in the plane of a pair of semicircular canals. The rotations are of low amplitude (10–20°) but of high acceleration (10000°/s²). If the peripheral vestibular system is intact and the vestibulo-ocular reflex (VOR) operates normally, the patient's eyes keep their fixations approximately on target (ie, gaze is held relatively stable in space). If not (ie, in the case of a reduced gain of the VOR towards the side of the head impulse), a reflexive saccade back to the examiner's nose is performed after the end of the head thrust. This corrective saccade indicates a peripheral vestibular hypofunction on the side towards which the preceding head rotation occurred, provided ocular motor function is intact.

Head impulses mainly drive the short latency, oligosynaptic VOR pathways from the semicircular canals to the extraocular muscles. Polysynaptic pathways via the cerebellum are less efficient in transmitting such high acceleration vestibular stimuli. The oligosynaptic pathways show distinct non-linear properties in that the contribution of the signals from the excited semicircular canals to the ocular motor response is greater than the contribution of the signals from the inhibited semicircular canals. This principle, known as Ewald's second law,² is probably the result of a non-linear pathway, which during high accelerations is driven into inhibitory cut-off on the

side of inhibited semicircular canals.^{3–4} In the case of unilateral peripheral vestibular hypofunction, Ewald's second law results in an asymmetric gain of the VOR (ie, the gain during high acceleration head rotations towards the lesioned side is lower than towards the healthy side).⁵

Halmagyi and Curthoys¹ as well as Foster and colleagues⁶ have shown surpassing accuracy of the bedside head impulse test (bHIT) in patients with complete unilateral vestibular loss. In these patients, both sensitivity and specificity reached 100% with reference to a control group of healthy subjects. In patients with partial vestibular deficits, however, the sensitivity of bHIT is considerably lower, because residual peripheral function results in a smaller gain asymmetry of the VOR. In a general clinical population of patients without and patients with significant asymmetries in caloric testing (canal paresis factor >25%), bHIT sensitivity was approximately 35% and bHIT specificity 95%.^{7–9} Direct comparison of bHIT with caloric testing, however, is problematic, as head impulses and caloric irrigation probe different frequencies of the VOR. Moreover, central compensation mechanisms in response to a peripheral vestibular deficit are frequency dependent and more often incomplete for higher (head impulses) than for lower frequencies (caloric irrigation).^{10–13}

Considering these problems of correctly appraising the clinical usefulness of bHIT by caloric testing, we set out to better determine the accuracy of bHIT by comparing it directly with head impulse testing that is assessed quantitatively from

Abbreviations: bHIT, bedside head impulse test; CI, caloric irrigation; qHIT, quantitative head impulse test; SCC, semicircular canals; VOR, vestibulo-ocular reflex

Table 1 Subjects whose video clips of bedside head impulses were presented to clinicians

Subject No	Age (y)	Aetiology	Gain right	Gain left	qHIT	Time (months)
1	27		0.94	0.80	N	
2	55	OT	0.29	0.48	B	60
3	56	VN	0.43	0.57	B	3
4	29		0.87	0.79	N	
5	26		0.91	0.88	N	
6	62	VN	0.76	0.56	L	6
7	46	VN	0.35	0.60	B	0
8	56	MD	0.73	0.58	L	120
9	26	VN	0.77	0.55	L	2
10	60	MD	0.62	0.47	B	8
11	49	VN	0.69	0.60	B	72
12	34	VN	0.46	0.50	B	0
13	42	VN	0.70	0.66	R	5
14	50		0.76	0.68	N	
15	81	OT	0.55	0.63	B	84
16	35		0.84	0.79	N	
17	44		0.93	0.82	N	
18	72	OT	0.60	0.62	B	120
19	24		0.85	0.89	N	
20	30		0.90	0.74	N	
21	71	VN	0.76	0.60	L	0
22	45	OT	0.64	0.58	B	96
23	35		0.79	0.66	N	
24	55	OT	0.37	0.41	B	48

Gain right, gain of the vestibulo-ocular reflex (VOR) during rightward head impulses.

Gain left, gain of the VOR during leftward head impulses.

Aetiologies of vestibular deficits were: vestibular neuritis (VN), Meniere's disease (MD) or ototoxicity (OT).

VOR gains of the quantitative head impulse test (qHIT) were normal (N), bilaterally decreased (B), decreased during rightward head impulses (R) or decreased during leftward head impulses (L).

Normal values were defined by values higher than the average gain minus 2 SDs in a population of healthy subjects (n = 37, average age 47 (SD 16) years).

The lower limits gains were 0.71 for rightward and 0.66 for leftward head impulses with the search coil mounted on the right eye.

Time, intervals between onset of the acute vestibular deficit to date of examination (months). Note that in healthy subjects the cells for Aetiology and Time are blank.

simultaneous recordings of eye and head movements with search coils. The result of this quantitative head impulse test (qHIT) was compared with the clinicians' evaluations of bHIT (presented on video clips) in the same patients. We further asked whether the sensitivities and specificities of bHIT differed depending on the clinicians' neuro-otological training.

MATERIAL AND METHODS

Definition

In this study, the term "head impulses" is used for horizontal head impulses, ie, rapid head rotations about the vertical axis with the subject sitting upright. As the horizontal semicircular canals (SCC) are not exactly orthogonal and the vertical SCC not exactly parallel to this axis, horizontal head impulses usually influence the activity in all SCC. The effect of horizontal head impulses, however, is largest on the horizontal SCC.

Subjects

Fifteen patients with bilateral (n = 10) and unilateral (right-sided n = 1; left-sided n = 4) peripheral vestibular hypofunction (average age 54 years) and nine healthy subjects (average age 33 years) were included in the study. Table 1 shows the subjects' characteristics. Patients were selected on the basis of results from the quantitative head impulse test (qHIT); attention was paid to assemble a population with a wide spectrum of different degrees of vestibular hypofunction (see supplemental data table E1; table E1 can be viewed on the *J Neurol Neurosurg Psychiatry* website at <http://www.jnnp.com/supplemental>). Informed consent of patients and healthy subjects was obtained after full explanation of the experimental procedure. The protocol was approved by a local ethics

committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki for research involving human subjects.

Head impulse testing

A video clip of the bHIT was recorded from each subject. For qHIT, eye and head movements were measured with scleral search coils. Both bHIT and qHIT were consecutively performed in each subject on the same day by the same experimenter, either one of two neurologists specialised in neuro-otology (DS, AP) or an experienced orthoptist (ES). Head impulses (amplitude 20–40°; duration 150–200 ms; peak velocity ~300°/s; peak acceleration ~10000°/s²) were applied approximately along the planes of the horizontal SCC (see Definition). The directions of the head thrusts were pseudo-randomly intermingled and <5–10 impulses were performed on each side. Subjects were instructed to always fix their eyes straight ahead on a light dot, located on a tangent screen 1.5 m ahead for qHIT or a dot just below the lens of the video camera during video recording.

Clinical head impulse testing (bHIT)

Video clips of bHIT in patients and healthy subjects were recorded with a Sony digital video camera recorder type DCR-PC100E, positioned ~1.5 m in front of the subject. Using Pinnacle Studio 9, Windows Media Video files (Microsoft) were produced (data rate 1308 kbps; video sample rate 24 bit). A DVD containing the 24 video clips was compiled and distributed to local and international clinicians (video clips can be seen online at <http://web.unispital.ch/neurologie/hit>). Before assessing the bHIT, participants were asked to view an introductory

video clip giving instructions about the identification of vestibular hypofunction by head impulses (see introductory video clip.mpg; introductory video clip.mpg can be viewed on the *J Neurol Neurosurg Psychiatry* website at <http://www.jnnp.com/supplemental>). The participants were then invited to view each video clip and indicate on an answer sheet whether they detected a unilateral deficit (right or left), a bilateral deficit or normal function. The video clips could be viewed as many times as necessary.

Evaluating clinicians were neurologists ($n = 37$; including one neuro-ophthalmologist and one advanced student in neurology), neurologists with at least 6 months of specialisation in neuro-otology ($n = 7$), otolaryngologists ($n = 8$) and otolaryngologists with at least 6 months of specialisation in neuro-otology ($n = 5$). The authors of this study did not serve as evaluators. To determine whether sensitivity and specificity of bHIT depended on the examiners' neuro-otological experience, clinicians were partitioned into an "expert" group ($n = 12$), which included neurologists and otolaryngologists trained in neuro-otology, and a "non-expert" group ($n = 45$), which included all other evaluators.

Quantitative head impulse testing (qHIT)

Eye and head movements were recorded in a magnetic frame (Remmel type system, modified by A Lasker, Baltimore, USA) using search coils (Skalar Instruments, Delft, the Netherlands), which were calibrated before each session (for details see Straumann and colleagues¹⁴). One search coil was placed on the right eye around the cornea (after anaesthetising the conjunctiva with oxybuprocaine 0.4%); the other was tightly fixed on the forehead with adhesive tape. Voltages were sampled with 16 bits at 1000 Hz and stored on the hard disk of a computer. Digitised signals were processed using interactive programs written in Matlab version 7.2. The gain of the vestibulo-ocular reflex g was computed by:

$$g = 1 - \frac{\Delta e_s(h_0; h_1)}{h_1 - h_0}$$

whereby h_0 and h_1 are head-in-space positions, and Δe_s is the difference between eye-in-space positions at $h_0 = 3^\circ$ and $h_1 = 7^\circ$.⁵ Of the 5–10 head impulses to each side, the median gain was chosen as the representative value (see supplemental data table E1 for median gain values of the 24 subjects; table E1 can be viewed on the *J Neurol Neurosurg Psychiatry* website at <http://www.jnnp.com/supplemental>). Head impulse tests were considered to be pathological if the median gain was below the lower normal limit of a population of healthy subjects, which serves as the reference database for routine clinical search coil head impulse testing in our laboratory ($n = 37$; average age 47 (SD 16) years). This lower normal limit is defined as 2 SDs below the average of the direction specific VOR gain measured in the reference population. With the coil on the right eye (as was the case in all 24 subjects tested in our study and in our reference population), lower normal limits are different for rightward and leftward head impulses; the lower normal limit for rightward head impulses is 0.71 and for leftward impulses 0.66. To date, we can only speculate on the factors leading to this normal gain difference. They may include differences between VOR pathways to the muscles of abducting and adducting eyes, artefacts resulting from dynamically asymmetric slippage of the search coil annulus on the conjunctiva or even the handedness of the operator causing systematic differences in the peak accelerations to the left and right. Placing the annulus on the left eye results in mirrored normal values (ie, the gain asymmetry cannot be due to a coil frame or amplifier artefact).

Effect of viewing distance on VOR gain

At the bedside, the typical distance between the subject's eyes and the visual target (ie, the tip of the clinician's nose) is ~ 0.5 m. In this study, however, the distance of the target (ie, the lens of the video camera and the laser dot on the tangent screen for search coil testing) was ~ 1.5 m. To keep a near target on the retina during head rotation, the gain of the VOR must increase compared with when the target is more distant because the reflex must also compensate for the translational movements of the eyes as they are placed anterior of the rotation axis of the head.^{15–17} Therefore, a VOR deficit during near viewing will lead to a larger retinal error and hence to larger correcting saccades. These larger rapid eye movements, in turn, may be better detectable by the clinician and increase bHIT accuracy. In view of the purpose of our study to compare bHIT and qHIT tested under the same stimulus conditions, we opted for similar viewing distances during both bHIT and qHIT. Note, however, that if one assumes that the yaw rotation axis of the head is 80 mm behind the centre of the eyes,¹⁸ the difference between ideal VOR gains for complete retinal stabilisation at 0.5 m (fixation of the clinician's nose) and at 1.5 m (fixation of the camera lens) target distances is only $\sim 10\%$ (ie, the impact of this factor on bHIT sensitivity is expected to be small).

Statistical analysis

To describe the frequency of assessing the bHITs as deficient as a function of their corresponding VOR gains measured quantitatively by search coils (qHIT), we fitted the following sigmoidal through the data cloud:

$$y = 100 \cdot \left(1 - \frac{1}{1 + e^{-a(x-c)}} \right)$$

where y is the percentage of evaluators rating bHIT as deficient at a specific VOR gain x of qHIT. The variables a and c were optimised by iteratively finding the best curve using non-linear least square fitting (Matlab function: `lsqcurvefit.m`). Bootstrapping (Matlab function: `bootstrap.m`) was used to compute the variability of the curve: 1000 random samples with replacement from the original data set were fitted in the same way as described above. The computed population of curves was used to obtain the distribution of bHIT evaluation percentages (y axis) at a specific qHIT gain value (x axis).

To analyse the accuracy of bHIT relative to qHIT, we computed the sensitivity and specificity of bHIT for each evaluator using the following formulas:

$$\text{bHIT sensitivity} = \frac{BQ_R}{BQ_R + bQ_R} + \frac{BQ_L}{BQ_L + bQ_L}$$

$$\text{bHIT specificity} = \frac{bq_R}{bq_R + Bq_R} + \frac{bq_L}{bq_L + Bq_L}$$

where

BQ_R is the number of subjects whose bHITs were rated pathological to the right side (including bilaterally deficient) and whose qHIT was pathological to the right side (including bilaterally deficient);

bQ_R is the number of subjects whose bHITs were rated normal to the right side (including bilaterally normal) and whose qHIT was pathological to the right side (including bilateral deficient);

bq_R is the number of subjects whose bHITs were rated normal to the right side (including bilaterally normal) and whose qHIT was normal to the right side (including bilaterally normal);

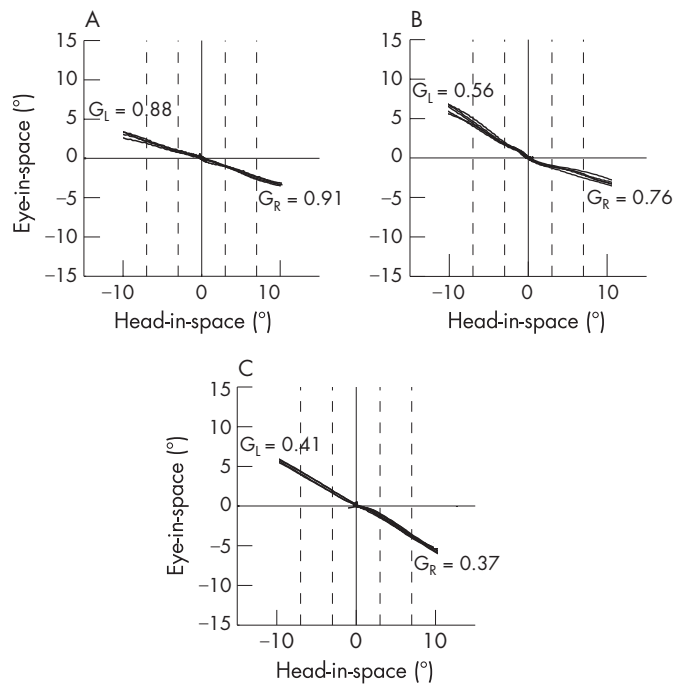


Figure 1 Examples of quantitative horizontal head impulses (qHIT) in subject No 5 (A), subject No 6 (B) and subject No 24 (C). If the vestibulo-ocular reflex (VOR) were perfectly compensatory, traces would be parallel to the abscissa (head-in-space axis); if the VOR were absent, traces would move on a 45° slope. G_R , median gain value for head impulses to the right; G_L , median gain value for head impulses to the left. Traces are clipped beyond 10° eccentricity of head-in-space. Broken vertical lines indicate intervals used to determine the gains (see Material and methods).

Bq_R is the number of subjects whose bHITs were rated pathological to the right side (including bilaterally deficient) and whose qHIT was normal to the right side (including bilaterally normal).

Definitions for leftward head impulses (Bq_L , bq_L , Bq_L) are analogous.

RESULTS

Figure 1 depicts typical examples of head and eye position traces during horizontal head impulses to both sides in three subjects (subject Nos 5, 6 and 24), as measured with search coils. Eye position in space ("eye-in-space") is plotted as a function of head position in space ("head-in-space"). In subject No 5 (fig 1A), a healthy control subject, gain values of the VOR were symmetric, but not completely compensatory, which to a certain degree is normal (see normal values). In subject No 6 (fig 1B), VOR gains were asymmetric with reduced gains for head impulses to the left. Thus, in this patient, peripheral vestibular function was reduced on the left side. In subject No 24 (fig 1C), VOR gains were bilaterally diminished (ie, peripheral vestibular hypofunction was bilateral).

For each of the 24 subjects participating in the study, fig 2 plots the results of bHIT as a function of qHIT. Head impulses to the right (fig 2A) and to the left (fig 2B) are shown separately, as normal values were found to be different between the qHIT to both sides (see Materials and methods). The median gain of unilateral head impulse tests for each subject gave the value on the x axis, and its corresponding value on the y axis was the percentage of evaluators rating the bHIT as deficient. Evaluators were divided into an "expert" and a "non-expert" group (criteria described in Material and methods). A sigmoidal function (see Material and methods) was fitted through the data cloud of experts and non-experts.

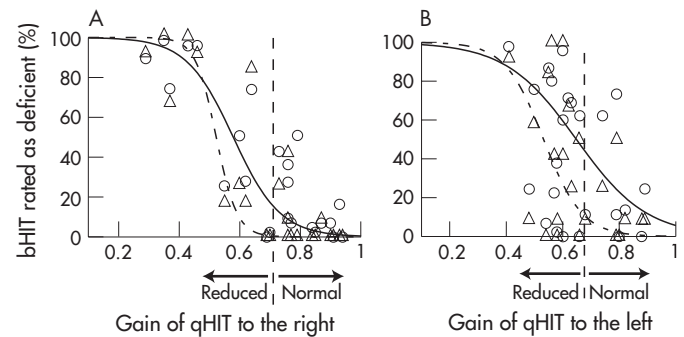


Figure 2 Results of bedside head impulse testing (bHIT) plotted as a function of quantitative head impulse testing (qHIT). Abscissa: gain of the vestibulo-ocular reflex during qHIT. Ordinate: percentage of evaluators who rated bHIT as deficient. (A) Head impulses to the right. (B) Head impulses to the left. Triangles: clinicians specialised in neuro-otology ("experts"; $n=12$). Circles: all other clinicians ("non-experts"; $n=45$). Dashed curve: sigmoidal function fitted through data cloud of experts; solid curve: sigmoidal function fitted through data of non-experts. Broken vertical lines: lower normal gain limit from a reference population of healthy subjects (average -2 SD). Note that normal lower limits for qHIT were found to be different between head impulses to the right (0.71) and to the left (0.66) (see Material and methods).

The fitted curves for the experts were shifted towards lower gains relative to the curves for the non-experts. In other words, experts tended to be more conservative in rating bHIT as pathological than non-experts. To quantify the difference between experts and non-experts, we determined the percentage of evaluators who rated the head impulses as pathological at exactly the lower normal limit of qHIT. For rightward bHIT, fitted sigmoidal curves crossed the lower normal gain limit ($g=0.71$) at 3.4% for experts and at 20.4% for non-experts; for leftward bHIT, curves crossed the lower normal limit ($g=0.66$) at 19.6% for experts and 36.7% for non-experts. To statistically test whether these numbers were different between both groups, we computed the percentages at which sigmoidal curves fitted through bootstrapped samples crossed the lower normal limits (see Material and methods). Unpaired t tests revealed highly significant ($p<0.001$) differences between experts and non-experts for both rightward and leftward head impulse tests.

Figure 3 compares bHIT sensitivity and specificity between experts and non-experts. Sensitivity (fig 3A) was lower for experts (average 63.3 (SD 8.8)%) than for non-experts (average 71.7 (SD 13.3)%) (ie, the latter correctly identified more vestibular deficits than experts). This difference was significant (unpaired t test: $p=0.044$). In contrast, specificity (fig 3B) was higher for experts (average 77.8 (SD 14.2)%) than for non-experts (average 64.2 (SD 16.2)%) (ie, the former misdiagnosed fewer vestibular deficits at the bedside when search coil head impulse tests were normal); 16% of the "experts" reached perfect specificity. The difference between both groups was again significant (unpaired t test: $p=0.011$). The same statistical comparison was repeated between neurologists, including neurologists with at least 6 months of specialisation in neuro-otology, and otolaryngologists, including otolaryngologists with at least 6 months of specialisation in neuro-otology (data not shown). Sensitivity and specificity did not differ significantly (unpaired t tests: $p>0.3$) between both groups (neurologists: sensitivity 69.1 (SD 12.8)%, specificity 75.8 (SD 15.8)%; otolaryngologists: sensitivity 66.2 (SD 12.9)%, specificity 72.9 (SD 16.5)%). Likewise, no significant (unpaired t tests: $p>0.4$) difference in sensitivity or specificity was observed between neurologists and otolaryngologists, when clinicians with at least 6 months of specialisation in neuro-otology were

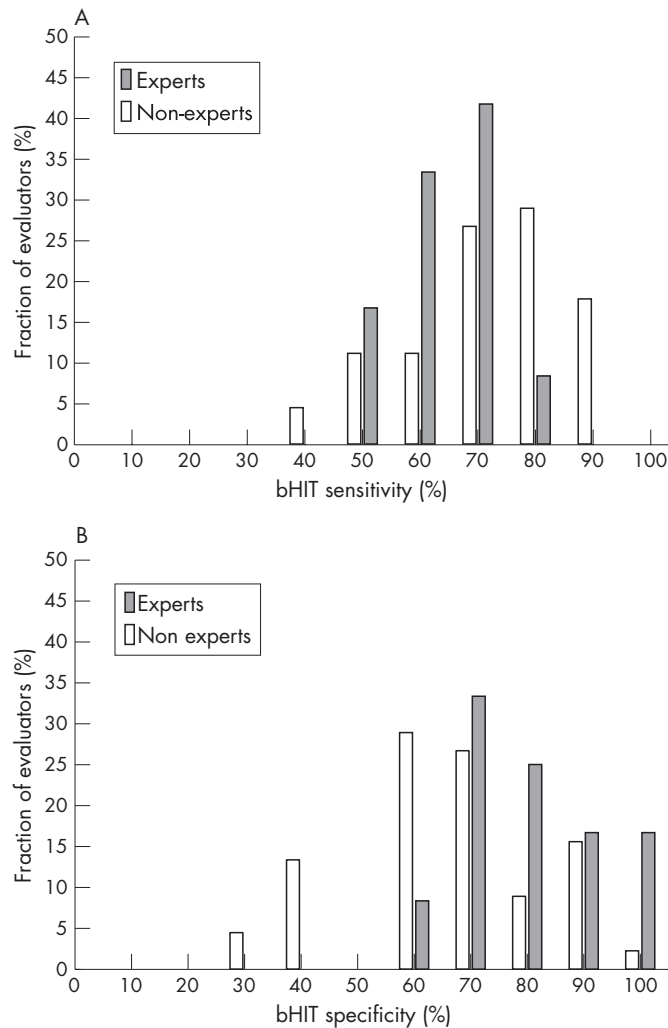


Figure 3 Comparison of bedside head impulse test (bHIT) sensitivity (A) and specificity (B) between experts and non-experts. Bin width: 10%.

excluded from both groups (neurologists: sensitivity 72.3 (SD 12.3)%, specificity 65.4 (SD 11.2)%; otolaryngologists: sensitivity 69.2 (SD 11.1)%, specificity 63.1 (SD 15.4)%). For all evaluators (experts and non-experts), average bHIT sensitivity was 69.9 (SD 12.9)% and average bHIT specificity 67.05 (SD 16.7)%.

DISCUSSION

We investigated the accuracy of the bHIT, a clinical manoeuvre that is widely used to assess peripheral vestibular function. To our knowledge, this is the first study that has validated the bHIT (presented on video clips) relative to qHIT, which we performed by simultaneous search coil recordings of eye and head movements. On average, bHIT sensitivity was 69.9% and bHIT specificity 67.05%. We found significant differences between “experts” (clinicians which had at least 6 months of training in neuro-otology) and “non-experts”.

Previous studies showed sensitivities and specificities of bHIT which differed considerably from the values found in our study. For example, Harvey and colleagues⁷ reported bHIT sensitivity of 35% and specificity of 95%. These authors concluded that the low sensitivity made bHIT inadequate as a screening tool for peripheral vestibular disease. Note, however, that Harvey *et al* compared the outcome of bHIT with results from binaural caloric irrigation (CI) and not with qHIT.

Beynon and colleagues⁹ also compared bHIT with CI. Sensitivity (34%) and specificity (100%) were similar as in the previous study. In addition, Beynon *et al* analysed bHIT sensitivity in subgroups of patients, who were partitioned according to the CI canal paresis factor. Only for severe canal paresis (>75%) was bHIT clinically useful with a sensitivity of 76.6%. For moderate canal paresis (50–75%), bHIT sensitivity reached only 9.5%. The authors predicted that bHIT would not replace caloric testing in the future.

Finally, Perez and Rama-Lopez¹⁹ plotted the receiver operating curve (bHIT sensitivity vs 1 minus bHIT specificity) with CI canal paresis as the independent variable and found the best cut-off point at a canal paresis factor of 42.5%. Applying this value as the normal CI limit, bHIT sensitivity was 78% and bHIT specificity 87%. Thus even after raising the normal limit of the canal paresis factor, a discrepancy between CI and bHIT remained. Accordingly, Perez and Rama-Lopez concluded that CI and bHIT are not redundant methods.

Based on these studies, CI does not appear to be the “gold standard” to assess the accuracy of bHIT. With CI as reference, bHIT sensitivity is vastly underestimated and its clinical use incorrectly undervalued. Apart from the cited literature, several other arguments support the notion that HIT (bHIT, qHIT) and CI probe different aspects of peripheral vestibular function and therefore complement each other. (1) HIT stimulates the VOR at high frequencies (up to 5 Hz), while CI stimulates the VOR at very low frequencies (~0.003 Hz).¹² (2) In the chronic state after vestibular neuritis, HIT remains deficient, while CI becomes frequently normal again (ie, central compensation mechanisms seem more effective at low VOR frequencies).^{5 10 20–22} (3) In roughly symmetrical bilateral peripheral vestibular hypofunction, the CI canal paresis factor gives a normal result while HIT correctly identifies the bilateral deficit.

We emphasise that it was not our intention to question the role of CI in the evaluation of patients with vertigo and balance disorders. CI and HIT should be regarded as complementary examinations. The purpose of this paper, however, was to compare bHIT with qHIT.

We found that bHIT sensitivity and specificity depend on the training of the examining clinician. Neuro-otological training of at least 6 months significantly decreased bHIT sensitivity but increased bHIT specificity. “Experts” are more inclined to rate bHIT as normal if its corresponding qHIT is slightly below the normal lower limit (see fig 2). To interpret this finding, one has to bear in mind that the clinician cannot visually track the reflexive ocular movement during the head impulse, since it lasts only about 150 ms. Rather, the clinician estimates the amplitude of the correcting saccade after the head impulse. Because the VOR gain is not perfect even in healthy subjects, small correcting saccades can often be observed despite intact labyrinths on both sides. Moreover, as clinicians tend to compare correcting saccades after head impulses to one side with correcting saccades after head impulses to the other side, physiological asymmetries of VOR gains might lead to the false assessment of a unilateral deficit. “Experts” seem to be more tolerant in accepting small correcting saccades as still normal. If a clinician views every correcting saccade as indicating a pathological HIT, bHIT sensitivity increases but specificity decreases. This association is exactly what we found in our “non-experts”.

An important caveat for the interpretation of deficient HIT concerns the complex relation between peripheral vestibular hypofunction and HIT towards the ipsilateral and contralateral sides. The physiology of linear and non-linear VOR pathways predicts a considerable gain reduction for contralesional HIT if compensation mechanisms are not engaged.²³ Generally, these central mechanisms are operational after a unilateral lesion, but

not always effective enough to bring the gain for contralesional HIT above the lower normal limit, especially in large unilateral hypofunction.⁵ Thus in unilateral peripheral vestibular hypofunction, HIT can be bilaterally impaired, although gains in these cases are generally asymmetrical with a lower gain for ipsilesional HIT. In other words, a bilaterally deficient HIT is not necessarily due to bilateral peripheral hypofunction. These considerations, however, concern both bHIT and qHIT; therefore, they do not constitute a factor that influences the sensitivity or specificity of bHIT compared with qHIT.

In conclusion, when qHIT is used as the “gold standard”, bHIT has an adequate sensitivity (average 69.9%) and therefore is clinically useful, provided the clinician receives at least minimal instruction (introductory video clip) on how to assess bHIT. We hypothesise that bHIT sensitivity could be even higher because of the shorter target distance at the bedside (ie, ~0.5 m between the subject's eyes and the tip of the nose of the experimenter) compared with our study (ie, ~1.5 m between the subject's eyes and fixation of the camera lens), which leads to an increase in VOR gain and consequently in amplitude of the correcting saccade (detailed explanation in the Material and methods section). Clinicians with neuro-otological experience have lower bHIT sensitivity (ie, are more conservative in rating bHIT as deficient) and higher specificity (ie, are better in identifying normal bHIT) than clinicians without this experience. This disagreement between experts and non-experts, however, was mainly restricted to those bHIT with corresponding qHIT gains slightly below the normal lower limit. Therefore, we advise ordering search coil head impulse testing or high speed video methods when bHIT is not conclusive.

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Deficient high-acceleration vestibular function in patients with polyneuropathy

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ABSTRACT

Background: Unsteadiness during standing and walking is a frequent complaint of patients with polyneuropathy (PNP).

Objective: To determine whether balance disorders in patients with PNP may be caused by reduced proprioceptive input from the feet alone or whether impaired vestibular input, resulting from involvement of the vestibular nerve, can be an additional factor.

Methods: A total of 37 patients (mean age 65 years \pm 12 SD; 12 women) with electrodiagnostically confirmed PNP (predominantly axonal: 18; predominantly demyelinating: 19) underwent horizontal search-coil head-impulse testing, which assesses the high-acceleration vestibulo-ocular reflex (VOR).

Results: Relative to a healthy comparison group, the gains (eye velocity divided by head velocity) of the horizontal VOR were reduced in 27 of 37 patients (unilateral: 13; bilateral: 14). The percentages of patients with unilateral or bilateral VOR deficits were not significantly different between patients with axonal or demyelinating PNP.

Conclusions: Two thirds of patients with axonal or demyelinating polyneuropathy (PNP) showed unilateral (~50%) or bilateral (~50%) gain reductions of the horizontal high-acceleration vestibulo-ocular reflex. This finding suggests that, in many patients with PNP, the neuropathic process includes the vestibular nerve. Such information is highly relevant for subsequent physical therapy, since vestibular exercise improves balance control and reduces disability. *Neurology*® 2009;72:2009-2013

GLOSSARY

CIDP = chronic inflammatory demyelinating polyneuropathy; **hVOR** = horizontal vestibulo-ocular reflex; **PNP** = polyneuropathy; **qHIT** = quantitative head-impulse test; **VOR** = vestibulo-ocular reflex.

It is generally assumed that postural imbalance and unsteadiness in patients with polyneuropathy (PNP) result from reduced somatosensory input to the brain from the distal part of the legs.¹ Additional vestibular impairment, however, could also play a role, i.e., imbalance in patients with PNP may be multisensory.² From a therapeutic perspective, the recognition of such an additional vestibular impairment is pivotal, because therapeutic strategies focusing on vestibular rehabilitation are able to improve postural stability.³⁻⁵

So far, a concomitance of peripheral neuropathy and vestibular impairment as determined by caloric irrigation has been described in two populations of patients with PNP. 1) Half of patients with auditory neuropathy and associated PNP showed reduced caloric vestibular responses.⁶ The positive family history in many of these patients hints at a possible hereditary vestibulo-cochlear syndrome associated with PNP. 2) Similarly, in half of patients with PNP with dizziness as the predominant symptom, caloric responses were unilaterally or bilaterally reduced.⁷ Limits for normal caloric responses used in this study, however, did not conform to a

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generally accepted standard. Overall, the inclusion criteria in both cited studies prevent drawing any conclusions about the prevalence of vestibular impairment in a general population of patients with PNP. Moreover, caloric testing, used in these studies to quantify vestibular function, assesses the vestibular system at a frequency range well below the frequencies relevant during daily live.⁸

To clarify the prevalence of vestibular impairment in unselected patients with predominantly axonal or predominantly demyelinating PNP, we conducted a prospective study using search-coil head-impulse testing, which assesses vestibular function at natural stimulus frequencies.^{9,10}

METHODS Participants were selected from patients referred to our academic neurologic center for further evaluation of polyneuropathic symptoms. Detailed history taking and complete neurologic examination were performed. Patients were specifically assessed for spontaneous and gaze-evoked nystagmus, correcting saccades following Halmagyi-Curthoys head impulses,¹¹ positional and positioning nystagmus, muscle atrophy and weakness, hyporeflexia and areflexia, as well as stand, gait, and limb ataxia. Sensory examinations included touch, pain, temperature, vibration, and position sense. Vibration sense was tested with a 128 Hz tuning fork at the ankles, knees, and index fingers and considered reduced at 4/8 or below. Patients were examined by two of the authors (A.S. and A.S.-P.).

All patients underwent both electroneurographic and electromyographic investigations. Independent of the clinical severity of symptoms, a consecutive 37 patients (65 ± 12 years; 12 women) with electrophysiologic signs of PNP, but no cerebellar impairment and no extraocular muscle palsy, were included in the study. Standard nerve conduction studies (motor and sensory) included the median, ulnar, sural, and peroneal nerves on both sides. If peroneal nerve conduction velocities ranged within normal limits or if distal peroneal compound muscle action potentials were not detectable, tibial nerves were also investigated. Electromyography was performed in the abductor digiti minimi, interosseus dorsalis I, and in the tibialis anterior muscles on both sides. If tibialis anterior muscle activity was normal, extensor digitorum brevis and abductor hallucis were additionally investigated. Axonal PNP was diagnosed in the presence of 1) marked amplitude reduction of compound sensory action potentials, 2) marked amplitude reduction of compound muscle action potentials, 3) no or only mild reduction in nerve conduction velocities, and 4) electromyographic signs of denervation. Conversely, demyelinating PNP was diagnosed in the presence of 1) marked prolonged distal motor latency of the compound muscle action potentials, 2) marked slowing of motor and sensory nerve conduction velocities, 3) abnormal temporal dispersion or motor conduction blocks, 4) relative preserved amplitudes of compound muscle action potentials upon distal stimulation, 5) marked prolonged latencies of F-waves, and 6) absence of electromyographic signs of denervation. If both axonal and demyelinating electrophysiologic signs were present, the classification of the patient (predominantly axonal or predominantly demyelinating) was based on the predominance of criteria. Age-related normative values were taken from Ludin.¹² Additional tests in all

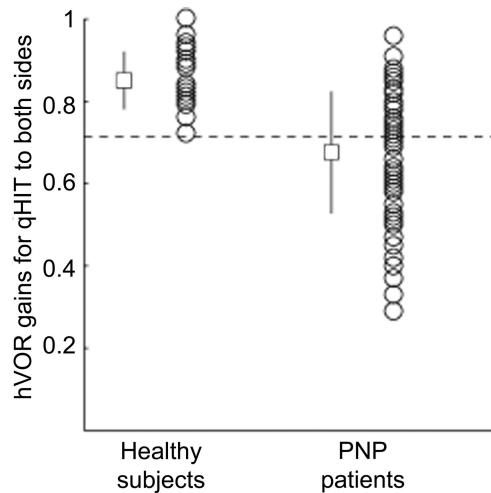
patients included serum protein electrophoresis, immunoelectrophoresis, and vasculitis screening. Independent of the clinical severity of PNP, CSF analysis was performed in all patients, which is standard procedure in our academic neurology department, unless the exact cause of the PNP is unambiguous after the clinical, electrophysiologic, and serologic assessments. Ten of 37 patients further underwent nerve and muscle biopsy, 10 of 37 patients cranial MRI, and 13 of 37 patients MRI or CT of the spine.

All patients were evaluated with the quantitative head-impulse test (qHIT). qHIT was performed by a technician who was unaware of the results of the electrophysiologic examinations. In all patients, qHIT was performed within 2 weeks of the electrophysiologic investigations. Eye and head movements were recorded in a magnetic frame (Remmel type system, modified by A. Lasker, Baltimore, MA) using search-coils, which were calibrated before each session.¹³ Horizontal head impulses (amplitude: $20-40^\circ$; duration: 150–200 msec; peak velocity: $\sim 300^\circ/\text{s}$; peak acceleration: $\sim 10,000^\circ/\text{s}^2$) were applied by an investigator standing behind the subject who was visually fixing upon a target light 1.24 m straight ahead. The directions of the head impulses were pseudorandomly intermingled and four to six impulses were performed in each direction. The gain of the horizontal vestibulo-ocular reflex (hVOR) was determined by computing the coefficient eye-in-space displacement divided by head-in-space displacement as head-in-space moved from 3° to 7° eccentricity from straight ahead.¹⁴ As the representative gain during head impulses to either side, the median value was computed. Median gain values were considered pathologic, if they were below two standard deviations of the average gain determined in a healthy control group. This group consisted of 14 healthy subjects (7 women; 25–75 y; 55 ± 15 y), who were selected by age frequency matching from a previously published population of 28 healthy subjects (15 women; 18–75 y, 44 ± 15 y).¹⁵ By this procedure we ensured that the average ages of patients and control subjects were not significantly different.

All subjects gave informed consent to participate in the study. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

RESULTS The average age of patients with PNP (12 women) was 65 ± 12 years (range 25–83) at the time of study enrollment. Average ages of patients with predominantly axonal (66 ± 10 y; $n = 18$, 8 women) and patients with predominantly demyelinating PNP (65 ± 13 y; $n = 19$, 4 women) were similar. Average duration of symptoms, as recorded in the medical histories, was 6.7 ± 5.5 years (range 1–20). Abnormal clinical findings on patients with PNP included the following: 1) unilaterally ($n = 12$) or bilaterally ($n = 10$) abnormal bedside head-impulse tests; 2) stand and gait ataxia ($n = 29$); 3) sensory deficits (touch: $n = 37$; pain: $n = 33$; temperature: $n = 33$; position: $n = 19$; vibration: $n = 25$); and 4) abnormal motor signs (muscle atrophy: $n = 20$; muscle weakness: $n = 19$; hyporeflexia or areflexia: $n = 33$ patients). The following etiologic factors for PNP were identified: diabetes mellitus ($n = 5$, 4 axonal), Waldenström macroglobulinemia ($n = 3$, none axonal), small-cell lung cancer paraneo-

Figure 1 Gains of the hVOR during head impulses to both sides in patients and healthy controls



On the left of each data point population, average values \pm SD are plotted. Horizontal dashed line: lower limit of gains for healthy subjects (average -2 SD). Note that average gain in patients with polyneuropathy (PNP) was significantly below that of healthy subjects, but many gains of patients with PNP were within the normal range. hVOR = horizontal vestibulo-ocular reflex.

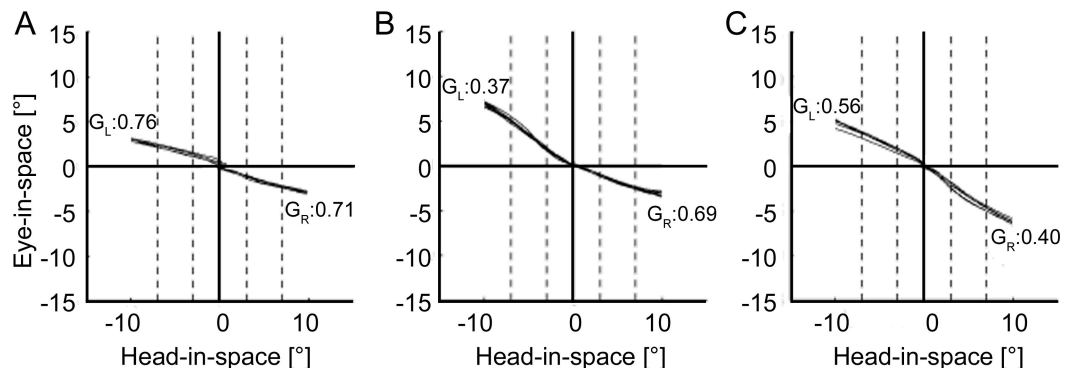
plastic disorder with positive anti-Hu antibodies ($n = 1$, axonal), cancer chemotherapy ($n = 2$, 1 axonal), hereditary disorders (hereditary motor and sensory neuropathy type II: $n = 2$), and chronic inflammatory demyelinating polyneuropathy (CIDP) ($n = 9$). In 15 patients (10 axonal), PNP was idiopathic.

Compared to healthy subjects, the average gain (eye velocity divided by head velocity) of the high-acceleration hVOR was reduced in patients with PNP (figure 1). Although many individual gain values recorded from patients with PNP during qHIT

to either side (two data points per subject) were in the normal range (above dashed line), the average gain value was below the average gain value of the healthy comparison group (comparison group: 0.85 ± 0.07 SD; patients with PNP: 0.67 ± 0.14 SD; unpaired two-tailed t test: $p < 0.01$). Overall, 27 patients (73%; 56 ± 24 y; 10 women) showed deficient hVOR gain values in one or both directions (unilateral: 13; bilateral: 14), while hVOR gain values to both sides were normal in 10 patients. Figure 2 depicts three typical examples of horizontal eye and head position traces during horizontal qHIT to both sides (A: normal hVOR gains in a patient with CIDP; B: unilaterally reduced hVOR gain in a patient with predominantly axonal PNP of unknown etiology; C: bilaterally reduced hVOR gains in a patient with CIDP).

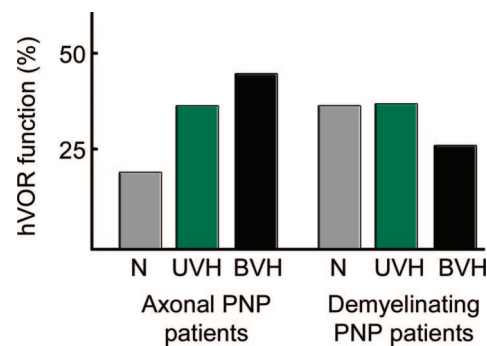
Average gain values during qHIT to either side were not significantly different between patients with predominantly axonal (0.66 ± 0.16 SD; $n = 18$) and patients with predominantly demyelinating (0.68 ± 0.13 SD; $n = 19$) PNP. Vestibular hypofunction was found in 81% of patients with predominantly axonal and in 63% of patients with predominantly demyelinating PNP (figure 3). The numbers of patients with bilateral normal gains, unilateral gain reduction, or bilateral gain reduction showed a distribution that was not different between both PNP groups (χ^2 test: $p = 0.69$, Fisher exact probability test: $p = 0.77$). When hVOR gains to both sides were averaged in each patient, values were abnormal in about half of the patients (predominantly axonal: 50%; predominantly demyelinating: 58%). The distribution of normal and abnormal average hVOR gains was not different between the two PNP groups (χ^2 test: $p = 0.63$, Fisher exact probability

Figure 2 Examples of qHIT to both sides in three typical patients with PNP



(A, C) Quantitative horizontal head-impulse tests (qHIT) in two patients with predominantly demyelinating polyneuropathy (PNP). (B) qHIT in one patient with predominantly axonal PNP. If the vestibulo-ocular reflex were perfectly compensatory, traces would be parallel to abscissa (head-in-space axis); if the vestibulo-ocular reflex were absent, traces would move on a 45° slope. G_R = median gain value for head impulses to the right; G_L = median gain value for head impulses to the left. Traces are clipped beyond 10° eccentricity of head-in-space. Dashed vertical lines indicate intervals used to determine the gains.

Figure 3 Gains of the hVOR in patients with predominantly axonal PNP and patients with predominantly demyelinating PNP



N = percentage of patients with normal gains to both sides; UVH = percentage of patients with unilateral gain reduction; BVH = percentage of patients with bilateral gain reduction; hVOR = horizontal vestibulo-ocular reflex; PNP = polyneuropathy. Note that distribution of percentages was not different between the two groups of patients as determined by Pearson χ^2 ($p = 0.69$).

ity test: $p = 0.74$). We also found no hVOR gain differences among subgroups of patients with different PNP etiologies, i.e., diabetic, paraproteinemic, paraneoplastic, toxic, hereditary, inflammatory and idiopathic (two-way analysis of variance: $p > 0.2$). Due to the relatively small number of patients in the respective subgroups, however, this finding can only be preliminary.

DISCUSSION In this prospective study, more than two thirds of patients with clinical and electrophysiologic signs of PNP showed an additional impairment of the hVOR. Thus, in many patients with PNP, the neuropathic process seems to involve the vestibular nerve. To assess the hVOR, we applied qHIT, which probes the vestibular system at frequencies that are relevant during locomotion and natural head movements. We therefore conjecture that imbalance, if present in patients with PNP, is frequently due to both proprioceptive and vestibular deficits, i.e., represents a multi-sensory balance disorder.

The percentages of unilateral and bilateral vestibular deficits were similar in patients with predominantly axonal and in patients with predominantly demyelinating PNP. This suggests that the vulnerability of the vestibular nerve is comparable in both classes of PNP. In contrast to a process of axonal damage, however, one would expect that demyelination would prolong the latency of the VOR, which normally ranges around 7–15 msec.¹⁶ With standard methods of latency measurements we could not find significant differences between the two groups of patients with PNP. More sophisticated methods of time series analysis and higher recording sample rates

(in this study: 1,000 Hz) might differentiate ocular responses from head impulses between the two PNP groups. Alternatively, brainstem auditory evoked responses may be more sensitive in detecting latency changes of the vestibulo-cochlear nerve.¹⁷

The strong association of PNP with vestibular dysfunction found in our study suggests a common pathomechanism. This impression is supported by a recent study in which 22% of patients with bilateral vestibulopathy were also diagnosed with PNP.^{18,19} Among the patients with bilateral vestibulopathy and PNP, about one third had additional cerebellar signs, which led the authors to speculate that the combination of vestibular, polyneuropathic, and cerebellar deficits may be due to a common neurodegenerative or autoimmune pathomechanism. The patients with PNP in our study lacked cerebellar signs; nevertheless, the association of vestibular and polyneuropathic deficits was evident. Possibly, there is a continuum between different combinations of polyneuropathic, vestibular, and cerebellar signs and symptoms, depending on the etiology and duration of the underlying disease.

The aim of our study was to detect an additional vestibular impairment in patients with PNP. The fact that patients with PNP were referred to an academic neurology department may represent a bias factor in neuropathic etiology and disease severity and consequently also in vestibular involvement. The surprisingly high percentage of deficient high-acceleration hVOR found in this study, however, should prompt more comprehensive neuro-otologic studies on patients with PNP, including turntable testing, caloric irrigation, vestibular evoked myogenic potentials, posturography, and auditory testing. Moreover, we advise clinicians to perform the bedside head-impulse test, which allows a reliable estimation of vestibular function outside the vestibular laboratory.^{11,20} The detection of an additional vestibular deficit impacts physical therapy, which then should include vestibular exercises to improve balance control. Physical therapy has been shown to enhance vestibular function and to improve compensatory proprioceptive and visual sensory strategies.^{4,5}

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Progressive Vestibular Impairment in Patients with Polyneuropathy

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It is generally assumed that imbalance in patients with polyneuropathy (PNP) results from deficient proprioceptive input arriving from the lower limbs. Polyneuropathic processes, however, may also impair vestibular function. In fact, we observed that two-thirds of patients with PNP show unilateral or bilateral impairment of vestibular function as assessed with search-coil head impulse testing. In the present work, we analyzed the same database of 37 polyneuropathic patients to find out whether the presence of a unilateral or bilateral vestibular deficit reflects a progression of the vestibular impairment. Results suggest that vestibular function in PNP patients deteriorates asymmetrically, first affecting one side and later both sides.

Key words: vestibulo-ocular reflex; neuropathy; head impulse test; vestibular nerve

Introduction

The Romberg sign is present when a patient, standing with feet together and eyes closed, tends to fall.¹ Usually, the sign is found in patients with polyneuropathy,^{2,3} myelopathy,⁴ vestibular deficit,⁵ or midline cerebellar disease.⁶

It is generally assumed that the Romberg sign and, more generally, imbalance in patients with polyneuropathy (PNP) result mainly from deficient proprioceptive input arriving from the lower limbs. A polyneuropathic process, however, may also involve the vestibular nerve.⁷ Thus, one can speculate that the Romberg sign in some polyneuropathic patients is caused by a combination of both proprioceptive and vestibular deficits.

Before considering this possibility, we need to know the prevalence of vestibular deficits in patients with PNP. So far, such information was only available for selected groups of polyneu-

ropathic patients with dizziness⁸ or auditory neuropathy.⁹ Yet, in a recent study, we found that in a general population of patients with PNP, two-thirds showed unilateral or bilateral impairment of vestibular function as assessed with search-coil head impulse testing.¹⁰ In the present work, we analyzed the same database to find out whether the unilateral or bilateral gain reduction of the vestibulo-ocular reflex would reflect a progression of the vestibular impairment in polyneuropathic patients.

Methods

Thirty-seven consecutive patients (12 female; 65 ± 12 y) with clinical and electrophysiological signs of polyneuropathy of various etiologies gave informed consent to participate in this study. The protocol was approved by a local ethics committee. Patients were evaluated with the quantitative head impulse test within 2 weeks of the electrophysiological investigations.

Eye and head movements were measured using dual search coils. Horizontal head impulses (amplitude: $20\text{--}40^\circ$; duration: 150–200

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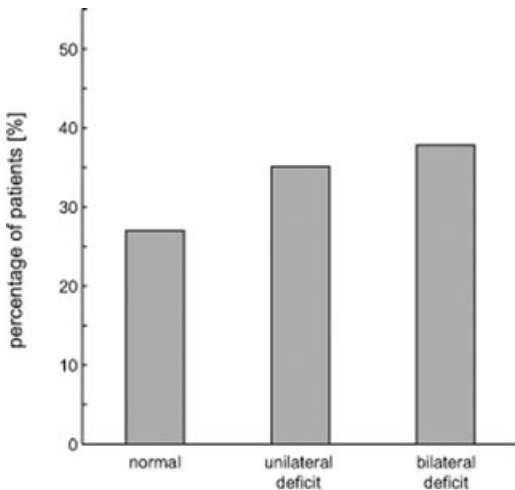


Figure 1. Distribution of polyneuropathic patients ($N = 37$) with normal vestibular function, unilateral vestibular deficit, and bilateral vestibular deficit. Vestibular function was assessed by search-coil head impulse testing in the horizontal direction.

msec; peak velocity: $\sim 300^\circ/\text{sec}$; peak acceleration: $\sim 10,000^\circ/\text{sec}^2$) were applied by the examiner standing behind the subject. Four to six head impulses were performed pseudorandomly in each direction. The gain of the horizontal vestibulo-ocular reflex was determined by computing the coefficient “eye-in-space displacement divided by head-in-space displacement” as head-in-space moved from 3° to 7° eccentricity from straight ahead.¹¹ As the representative gain during head impulses to either side, the median value was computed. Median gain values were considered pathological if they were below two standard deviations of the average value collected from a healthy control group.

Results

Two-thirds of patients with PNP showed abnormally reduced gains of the vestibulo-ocular reflex (VOR) during horizontal head impulses to one or both sides (Fig. 1). Among the patients with abnormal VOR gains, about half presented with a unilateral and about half with a bilateral deficit.

The duration from the occurrence of the first PNP symptoms to the testing was 5 years (± 5.5 SD). There was no significant ($P > 0.05$) rank correlation (Spearman) between this duration and horizontal VOR gains (data not shown). Similarly, the average duration of polyneuropathic symptoms was not different among the three groups with normal gains, unilaterally reduced gains, and bilaterally reduced gains (one-way ANOVA: $P > 0.05$).

Since the rate of PNP progression shows large interindividual differences and may not exactly parallel the rate of VOR gain reduction, we cannot be certain whether the vestibular disorder in PNP patients is also progressive. For a conclusive answer, we would have to perform a prospective longitudinal study over many years. We may, however, conjecture that the three groups of patients represent a continuum of progressive vestibular impairment during which initially no side, later one side, and finally both sides show an abnormally low VOR gain during head impulse testing. In this case, the gain of the more affected side should be higher in PNP patients with unilateral gain reduction than in patients with bilateral gain reduction. This, in fact, is the case (Fig. 2); the VOR gain of the side with the lower gain decreases when analysis “advances” from healthy subjects to PNP patients with normal gains, PNP patients with unilaterally decreased gains, and, finally, PNP patients with bilaterally decreased gains.

Discussion

Our data demonstrate that disorders leading to polyneuropathy (PNP) seem to involve vestibular function in many patients. We also found that the vestibulo-ocular reflex in patients with bilateral gain reduction during horizontal head impulses was more affected than in patients with a unilateral deficit. This suggests a rather asymmetric progression of the vestibular impairment that first affects one side and later both sides.

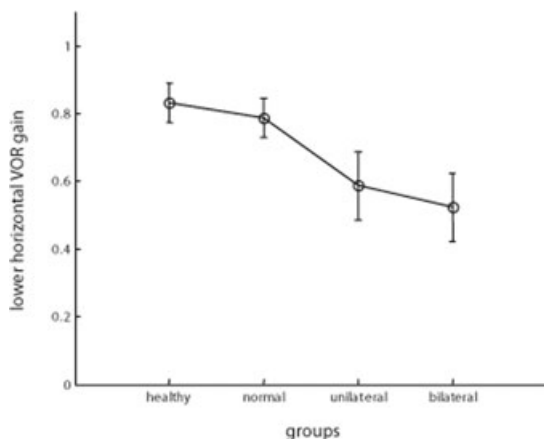


Figure 2. Average gains (± 1 SD) of the vestibulo-ocular reflex during horizontal search-coil head impulse testing in healthy subjects as well as in polyneuropathic patients with normal vestibular function, unilateral vestibular deficit, and bilateral vestibular deficit. For each subject the lower of the two horizontal gains (rightward or leftward) was used to compute the population average. Note the decrease of average gains from left to right. While the difference between patients with normal gains and patients with unilateral or bilateral deficit was significant ($P < 0.05$), this was not the case ($P = 0.1$) between patients with unilateral and patients with bilateral deficit (one-way ANOVA).

In view of these results, clinicians should always consider an additional vestibular deficit in PNP patients with imbalance, especially if the Romberg sign is present. Unless the cause of the polyneuropathic process is treated, vestibular deficits seem to increase with time.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Vestibular and auditory deficits in Fabry disease and their response to enzyme replacement therapy

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Abstract Progressive hearing (pHL) and vestibular (pVL) loss are frequent deficits in Fabry disease (FD). Recently, enzyme replacement therapy (ERT) with human α -galactosidase A has become available. Here, we investigate the association between pHL and pVL in FD and their ERT responses. Pure tone audiometry (PTA) and head impulse testing (HIT) were administered at baseline in 47 patients (25 male, 18–60 y; 22 female, 17–74 y), of whom 24 also received caloric irrigation (CI). Of the 47 patients, 38 (24 male) were tested both before and during ERT (follow-up ≤ 60 months). ERT consisted of agalsidase alfa infusions. At baseline, pHL was present in 88 % of males and 86 % of females. Over all tested frequencies (range: 0.5–6 kHz), pHL was significantly (two-way ANOVA: $p < 0.05$) greater at higher age and in males, with largest deficits at high frequencies. When assessed with HIT, 80 % of males and 77 % of females had pVL. pVL was significantly greater at higher age and in males. Tested

with CI, 21 % of males and 0 % of females had pVL. No associations among individual semicircular canal (SCC) deficits, as tested by HIT, and hearing was observed in individual ears. After ≥ 18 months of ERT, pVL was significantly smaller than at baseline (ANOVA for HIT: $p < 0.01$). In contrast, pHL remained unchanged by ERT over 60 months ($p > 0.05$). We conclude that pHL and pVL prevalences are similar in FD. To detect pVL, HIT is more sensitive than CI. We speculate that pHL and pVL emerge from lesions within the vestibulo-cochlear labyrinth, because no specific patterns of vestibulo-cochlear deficits were observed, as expected if lesions were more proximal along the inferior or superior branch of the vestibulo-cochlear nerve or labyrinthine artery. Finally, ERT stabilizes auditory and even improves vestibular function.

Key words lysosomal disease · Fabry disease · head impulse test · caloric irrigation · pure tone audiogram

Introduction

In Fabry disease, an X-linked lysosomal storage disorder, deficient activity of the enzyme α -galactosidase A (α -Gal A) [6, 22] leads to intracellular accumulation of globotriaosylceramide predominantly in the vascular

tissue, eye, skin, kidney, heart, and nervous system [7, 10]. Disease prevalence is estimated between 1:40,000 and 1:117,000 live births [27]. If later-onset variant phenotypes are included, incidence ranges from 1:3100 to 1:4600 [39]. The clinical onset in childhood is characterized by painful acroparaesthesias, hypohydrosis, typical angiokeratoma, gastrointestinal symptoms, such as ab-

dominal pain and diarrhea, and corneal dystrophy [7, 10, 26]. Renal failure, cardiomyopathy, and cerebrovascular disease cause premature death, on average about two decades earlier than in the general population [24–26]. Although inheritance is X-chromosomal linked, females can be affected to a mild or severe degree due to random X-chromosomal inactivation [42]. Recently enzyme replacement therapy (ERT) with recombinant or gene-activated human α -Gal A provided evidence of reversibility of several clinical manifestations, notably of cardiac, renal, and peripheral neuropathic symptoms [5, 11, 19, 36, 40, 43].

Hearing loss has often been linked with Fabry disease, but only recent studies have ascertained its high prevalence [9, 18, 26]. Predominantly, hearing loss in Fabry disease is of sensorineural type [14, 15, 18, 34]. Likewise, vestibular function seems to be commonly affected in Fabry disease, but so far only small case series are available [9, 29, 32]. When cochlear and vestibular impairments in patients with Fabry disease are compared, hearing loss is more frequently reported than vestibular loss and an independent involvement between the cochlea and the vestibular labyrinth has been suggested [9, 29]. While studies agree on the prevalence of hearing loss, the prevalence of vestibular impairment varies considerably, i.e. ranges from 30% [9] to 50% [29] when tested with caloric irrigation, and up to 70% when tested with search-coil head impulses [32].

Caloric irrigation and the search-coil head impulse test are both validated assessments of peripheral vestibular function. The advantage of the search-coil head impulse test over caloric irrigation consists in a more physiological stimulation of the high-frequency range of the vestibular system and the possibility to determine the function of individual semicircular canals [3, 4, 37].

The present study was prospectively conducted in Fabry patients with the following goals: 1) to determine the prevalence of auditory and vestibular impairments in male and female patients; 2) to compare vestibular responses as tested by head impulses and caloric irrigation; 3) to correlate vestibular function to hearing; 4) to determine the effect of ERT on vestibular and auditory function.

Subjects and methods

Subjects

Forty-seven patients (25 male, 18–60 y, mean 40 y; 22 female, 17–74 y, mean 34 y) diagnosed with Fabry disease (FD) were vestibularly and audiotically tested at baseline examination. The diagnosis of FD was confirmed in all patients by enzyme assay or DNA analysis. Patients were consecutively recruited starting February 2001. Vestibular assessments at baseline included head impulse testing in all 47 patients, of whom 24 patients (16 male, 18–60 y, mean 41 y; 8 female, 17–74 y, mean 44) also received caloric irrigation. Enzyme replace-

ment therapy (ERT) was given to 38 (24 male) of the 47 patients. All FD patients receiving ERT were tested at relatively regular intervals during a period of up to 60 months. ERT consisted of intravenous infusions of gene-activated or recombinant human α -galactosidase A. Agalsidase alfa (Replagal®; TKT Europe – SS, Danderyd, Sweden) was given at a dose of 0.2 mg/kg every two weeks. The comparison group for vestibular head impulse testing comprised 28 healthy subjects (13 male; aged 18–75 y, mean 44), while normal values for audiometric testing were taken from ISO 7029¹, an internationally accepted age- and gender-matched control data set. Informed consent was obtained from patients and healthy human subjects after a full explanation of the experimental procedure. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki for research involving human subjects.

Auditory testing

Routine pure tone audiometry was performed for auditory assessment. The audiometric type, amount, and configuration of hearing loss were further analyzed. The type of hearing loss was classified as sensorineural (average air-bone gap of less than 15 dB for 0.5, 1 and 2 kHz), conductive (normal bone conduction thresholds and average air-bone gap of 15 dB or more for 0.5, 1, and 2 kHz), or mixed (bone conduction threshold greater than 20 dB HL in combination with averaged air-bone gap 15 dB or more for 0.5, 1, and 2 kHz) according to the European Working Group on Genetics and Hearing Impairment.² Hearing loss was categorized according to pure-tone air conduction thresholds at 0.5, 1, 2, 4, and 6 kHz relative to 90th percentiles of the age- and gender-matched ISO 7029 control data. To determine the shape of audiometric configurations, we computed the following thresholds (T) for each of the two ears in every patient:

low frequency threshold: $T(\text{low}) = [T(0.5 \text{ kHz}) + T(1 \text{ kHz})]/2$

mid frequency threshold: $T(\text{mid}) = T(2 \text{ kHz})$

high frequency threshold: $T(\text{high}) = [T(4 \text{ kHz}) + T(6 \text{ kHz})]/2$

Using these three thresholds, audiometric configurations were defined as follows (modified definitions from European Working Group on Genetics and Hearing Impairment² and [9]):

- *flat*: $|T(\text{low}) - T(\text{mid})| \leq 15 \text{ dB HL}$ AND $|T(\text{mid}) - T(\text{high})| \leq 15 \text{ dB HL}$
- *mid frequency U-shaped*: $|T(\text{mid}) - T(\text{low})| > 15 \text{ dB HL}$ AND $|T(\text{mid}) - T(\text{high})| > 15 \text{ dB HL}$
- *high frequency*: $|T(\text{high}) - T(\text{low})| > 15 \text{ dB HL}$ AND $|T(\text{mid}) - T(\text{low})| < [T(\text{high}) - T(\text{low})]/3$
- *sloping*: $|T(\text{high}) - T(\text{low})| > 15 \text{ dB HL}$ AND $|T(\text{mid}) - T(\text{low})| > [T(\text{high}) - T(\text{low})]/3$
- *low frequency*: $|T(\text{low}) - T(\text{high})| > 15 \text{ dB HL}$ AND $|T(\text{mid}) - T(\text{high})| < [T(\text{low}) - T(\text{high})]/3$
- *rising*: $|T(\text{low}) - T(\text{high})| > 15 \text{ dB HL}$ AND $|T(\text{mid}) - T(\text{high})| > [T(\text{low}) - T(\text{high})]/3$

¹ International Organization for Standardization (2000). Acoustics – Statistical distribution of hearing thresholds as a function of age, ISO 7029:2000

² <http://www.gendeaf.org>. Recommendations for description of genetic and audiological data for families with nonsyndromic hereditary hearing impairment; Composed by the GENDEAF study group on genotype phenotype associations

■ Vestibular testing

Caloric irrigation was performed according to the Fitzgerald-Hallpike testing protocol [13]. In sequence, unilateral 30 °C-cold and 44 °C-warm water irrigations during 20 s with 20 mL of water were performed on either side and eye movement responses were video-oculographically recorded for 180 s [37]. The asymmetry of peripheral vestibular function in percent, i. e. the canal paresis factor, was determined by Jongkees formula [21]. For quantitative head impulse testing, three-dimensional eye and head movements were measured in a magnetic frame (Remmel type system, modified by A. Lasker, Baltimore, MA, USA) using dual search-coils. Search-coils were calibrated before each session [41]. After anesthetizing the conjunctiva with oxybuprocaine 0.4 %, one search-coil was placed on the right eye around the cornea and the other was tightly fixed on the forehead with adhesive tape. Voltages were sampled at 16 bits at a frequency of 1000 Hz and stored on the hard disk of a computer. During experiments, subjects were seated inside the magnetic coil frame (side length: 1.4 m). Care was taken to position the center of the inter-pupillary line in the center of the magnetic frame. Rotational head thrusts (amplitude: 20–40°; duration: 150–200 ms; peak velocity: ~ 300 °/s; peak acceleration: ~ 10000 °/s²) were applied approximately along the planes of the horizontal, left anterior and right posterior (LARP), and right anterior and left posterior (RALP) semicircular canals by an investigator standing behind the subject. The directions of the head impulses were pseudorandomly intermingled and four to six impulses were performed in each direction. For each semicircular canal in the appropriate stimulus plane, the gain of the vestibulo-ocular reflex (VOR) was determined by computing the coefficient 'eye-in-space displacement divided by head-in-space displacement' with head-in-space moved from 3° to 7° eccentricity from straight-ahead [31]. Note that a decreased gain value in the direction of an individual semicircular canal does not necessarily imply that the pathology is within this canal; the pathology could as well be somewhere along the primary vestibular afferents from this semicircular canal.

■ Statistical analysis

To analyze the interference between the patterns of auditory and vestibular damage, we used chi-square testing. Wilcoxon rank sum test for equal medians was performed to determine the effect of age on the high frequency vestibulo-ocular reflex as tested by head impulses in healthy controls. The effects of age and gender on vestibular and audiometric data at baseline data were analyzed with two-way analysis of variance (ANOVA). Two-way ANOVA was also used to determine whether semicircular canals for vestibular function or frequencies for audiometric functions were differentially affected by FD. If the outcome of the two-way ANOVA was statistically significant, we performed multiple comparisons testing to discern the grouping variables that differed significantly. To compare baseline data between different groups (e. g. males vs. females), we applied unpaired t-tests. Effects of ERT at different time intervals were evaluated by one-way ANOVA. If the outcome of ANOVA testing was statistically significant, we performed multiple comparison testing to determine, between which periods of ERT significant differences occurred.

Results

■ Vestibular and auditory function at baseline

Fig. 1 depicts measures of vestibular (head impulse testing) and auditory (pure tone audiography) function in a typical patient with Fabry disease (U. H.; age: 44 years). For head impulses along the horizontal plane, gains of

the vestibulo-ocular reflex (VOR) were bilaterally reduced (Fig. 1A), reflecting hypofunction of the horizontal semicircular canals (SCC) on both sides. Along the RALP (= right anterior, left posterior) plane, VOR gains were reduced for upward head impulses and normal for downward head impulses (Fig. 1B), corresponding to reduced left posterior SCC and normal right anterior SCC function. VOR gains along the LARP (= left anterior, right posterior) plane were reduced in both directions (Fig. 1C), i. e. both left anterior SCC and right posterior SCC functions were reduced. In this patient, caloric irrigation revealed a normal vestibular function (canal paresis factor: 16%; data not shown). Pure-tone audiometry demonstrated bilateral high-frequency hearing loss with a mean high-frequency loss (air conduction at 4 and 6 kHz) of 35 dB for the right and 67.5 dB for the left ear (Fig. 1D). However, when these audiometric data were corrected for age (ISO 7029, see Methods), the high-frequency hearing loss was restricted to the left ear (with 18.5 dB above the mean of the 90th percentiles for 4 and 6 kHz). Thus, in this Fabry patient, vestibular deficits were found on both sides, while hearing function was impaired on one side only.

Fig. 2 shows the percentages of male (left bars) and female (right bars) patients (N=47; male=25) with vestibulo-auditory impairment at baseline examination assessed by head impulse testing along different semicircular canal planes (HSCC: horizontal semicircular canals; ASCC: anterior semicircular canals; PSCC: posterior semicircular canals), caloric irrigation (CP: canal paresis factor), and pure tone audiometry (Audio). Bars indicating the percentage of bilateral (gray area) and unilateral (white area) deficits are piled. For example, the horizontal semicircular canals (Fig. 2, leftmost bar) were affected bilaterally in 20 % and unilaterally in 48 % of male patients. For caloric testing, only the percentage of patients with a pathological canal paresis factor – a measure of peripheral vestibular asymmetry (see Methods) – is depicted (white area), since no generally accepted parameter for bilateral impairment assessed by caloric irrigation is available. Recall that caloric irrigation was only performed in 24 patients (16 male), while head impulses and pure tone audiometry were completed in all 47 patients.

Altogether, in 80 % of male and 77 % of female patients, head impulse tests in at least one of six semicircular canal directions were abnormal. Pathological asymmetries of caloric responses, i. e. with a canal paresis factor > 25 %, were found in 21 % of male and in none of female patients. Thus, vestibular deficits were more frequently identified with search-coil head impulse testing than with caloric irrigation. In pure tone audiometry, 88 % of male and 86 % of female patients showed impaired auditory function compared to age- and gender-matched ISO control data. Hearing impairment was sensorineural in all affected patients, i. e. no con-

Fig. 1 Example of head impulses along the horizontal (A), RALP (= right-anterior & left-posterior semicircular canals) (B) and LARP (= left-anterior & right-posterior semicircular canals) (C) planes as well as pure tone audiometry (D) in a typical patient with Fabry disease (U. H.; age 44 y) at baseline examination. A, B, C If the vestibulo-ocular reflex (VOR) were perfectly compensatory, traces would be parallel to the abscissa (head-in-space axis); if the VOR were absent, traces would move on a 45° slope. Traces are clipped beyond 10° eccentricity of head-in-space. Dashed vertical lines indicate intervals used to determine the gains (see Methods). g: median gain value during head impulses. D Pure tone audiogram. Circles: hearing thresholds of the right ear; crosses: hearing thresholds of the left ear

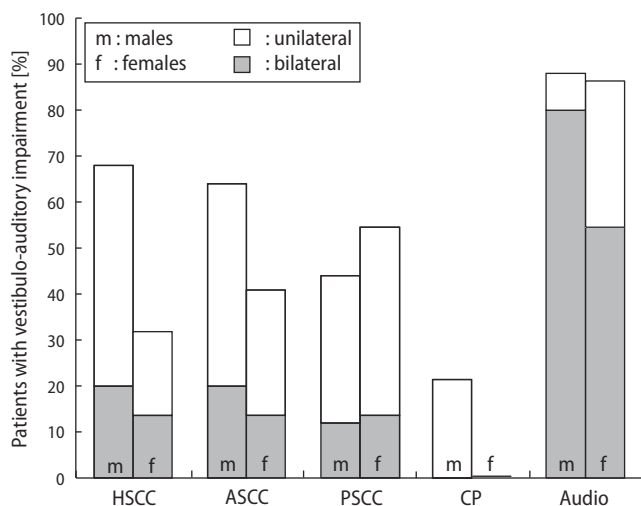
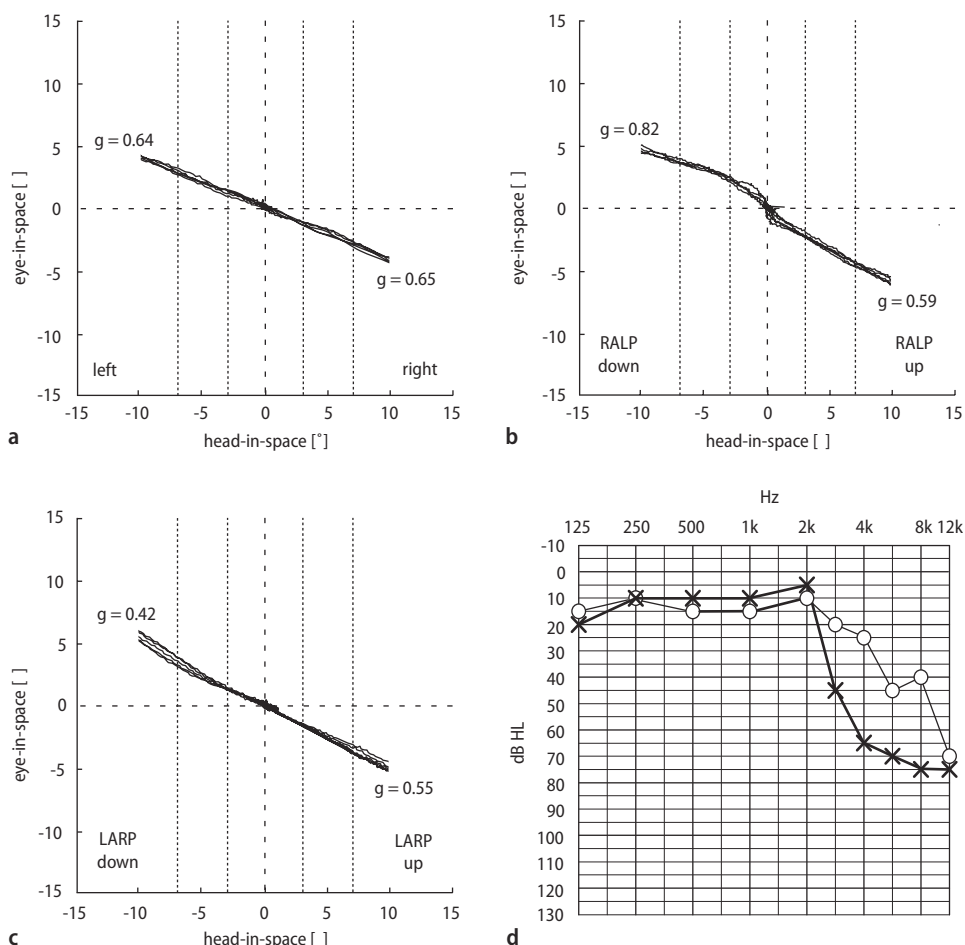


Fig. 2 Percentages of male (left columns; N = 25) and female (right columns; N = 22) patients at baseline examination with unilateral (white area) and bilateral (gray area) vestibular and auditory impairments. Horizontal (HSCC), anterior (ASCC), and posterior (PSSC) semicircular canal function assessed with search-coil head impulse testing. CP canal paresis factor, i. e. asymmetry of the vestibular function tested by caloric testing. Audio pure tone audiometry (hearing loss relative to ISO)

ductive or mixed hearing impairment was observed. Configurations of audiometric thresholds were high-frequency in 40% of males and 9% of females, flat in 52% of males and 86% of females, and sloping in 8% of males and 5% of females (see Methods for definitions).

■ Relation between vestibular and auditory deficits at baseline

We asked whether there was an association between vestibular and hearing impairments in Fabry patients at baseline. Table 1 compares vestibular (as assessed with head-impulse testing) and auditory function in the pooled population of male and female patients. Clearly, vestibular function did not always parallel auditory function, i. e. a vestibular deficit in a patient did not imply a hearing impairment in the same patient, and vice versa (chi square: $p > 0.05$). Likewise, no association between vestibular and auditory function was found when analyzing data from males and females separately (data not shown).

As demonstrated in Table 2, there was not even an as-

Table 1 Vestibular and auditory function of either ear in Fabry patients assessed by search-coil head impulse testing and pure tone audiometry

Auditory function (no. of patients)	Vestibular function (no. of patients)		Total
	normal	affected	
normal	2	4	6
affected	8	33	41
total	10	37	47

Number of Fabry patients with normal or abnormal auditory or vestibular function. Significance of chi square: $p > 0.05$

Table 2 Right- and left-ear vestibular and auditory function in Fabry patients assessed by search-coil head impulse testing and pure tone audiometry

Auditory function (no. of ears)	Vestibular function (no. of ears)		Total
	normal	affected	
normal	9	12	21
affected	28	45	73
total	37	57	94

Number of ears in Fabry patients with normal or abnormal auditory or vestibular function. Significance of chi square: $p > 0.05$

sociation between vestibular and auditory function at the level of ipsilateral labyrinths or their afferents. Whether or not a Fabry patient had a vestibular deficit on one side (as assessed with head-impulse testing) was independent of the presence of an auditory deficit on the same side, and vice versa (chi square: $p > 0.05$). Also separate analyses among male and female patients found no association between vestibular and auditory function on the same side (data not shown).

Fig. 3 compares patterns of ipsilateral vestibular and auditory deficits of Fabry patients (results from right and left sides are pooled). 32 % of patients showed typical patterns of vestibular and auditory deficits that are expected if lesions were situated along the branches of the vestibulo-cochlear nerve or labyrinthine artery [12, 33]. These patterns include 1) horizontal and anterior SCC deficits, 2) posterior SCC and hearing deficits, and 3) deficits of all SCC and hearing. In the majority of patients (68 %), however, no pattern was identifiable.

■ Factors determining vestibular and auditory function at baseline and its characteristics during ERT

To statistically analyze the influence of age and gender on vestibular function, we first computed the average VOR gain of head impulse testing along the three ipsilateral semicircular canals of each ear in every patient. This average VOR gain was then normalized by sub-

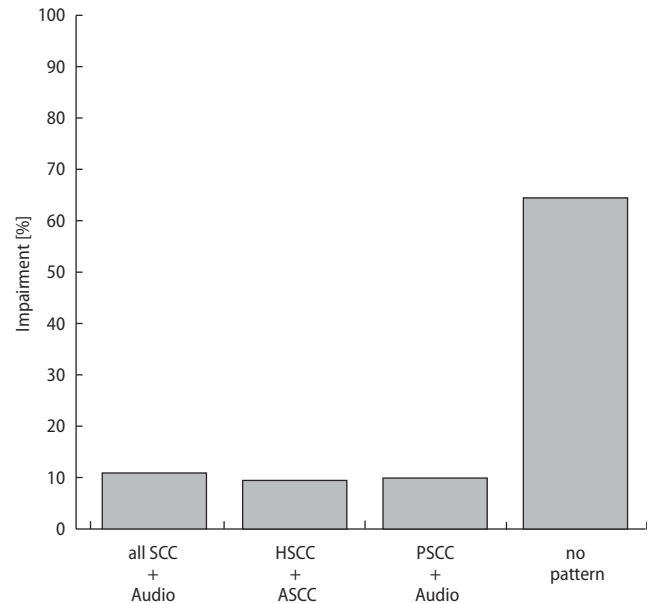
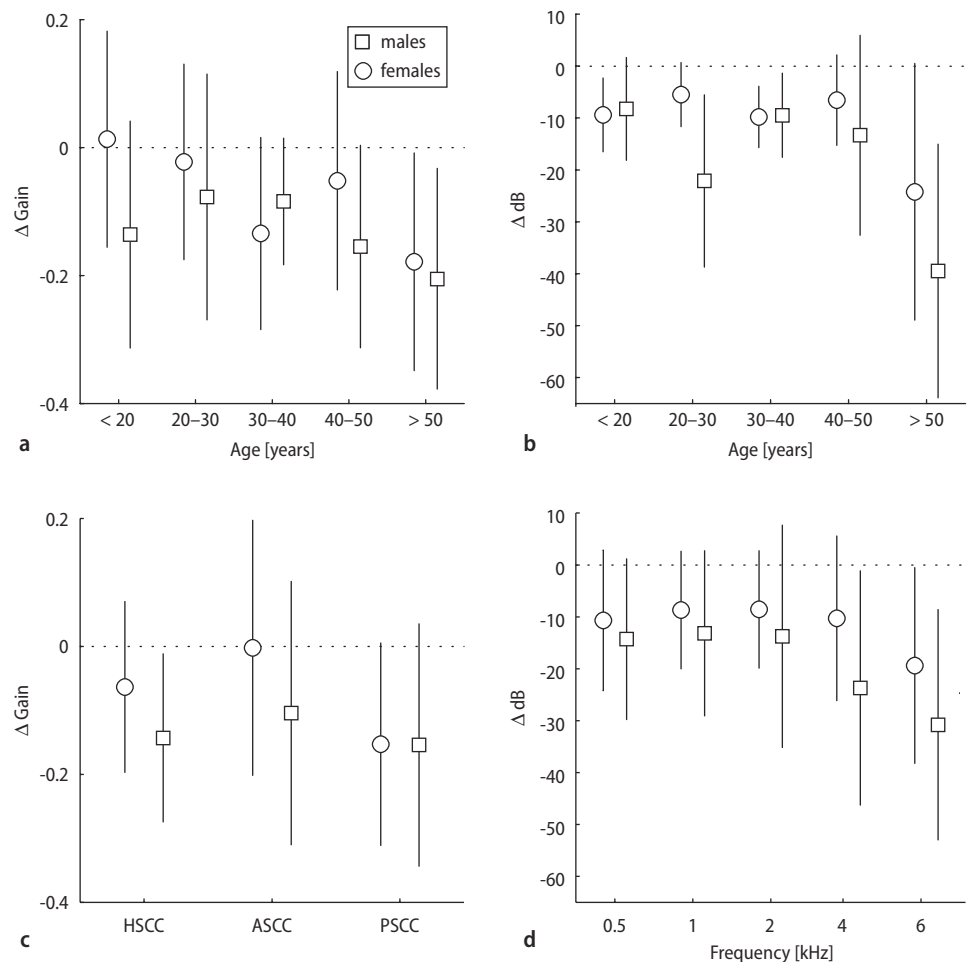


Fig. 3 Percentages for patterns of impaired semicircular canal (SCC) and auditory function within the same ear, as expected by different topographical locations of lesions due to impairments of labyrinthine nerve or blood supply or lesions within the labyrinth. All: impairment of all three SCC and hearing within the same ear; $N = 11$. *HSCC + ASCC* deficit of the horizontal and anterior SCC as expected from a lesion along the superior branch of the vestibular nerve or labyrinthine artery; $N = 9$. *PSCC + Audio* deficit of the posterior SCC and auditory function as expected from a lesion along the inferior branch of the vestibular nerve or labyrinthine artery; $N = 10$. *No pattern* no association of the three SCC and auditory function; $N = 64$

tracting the grand average of unilateral VOR gains in the healthy control group. Since average unilateral VOR gains in our group of healthy subjects did not significantly decline with age (Wilcoxon rank sum test for equal median $p > 0.05$), gain values of Fabry patients were not age-corrected. Two-way analysis of variance (ANOVA) demonstrated a significant ($p < 0.01$) influence of age and gender on vestibular function in the Fabry patients. Fig. 4A illustrates that vestibular function in Fabry patients declines with age, i. e. the duration of the disease, and is more reduced in male (squares) than in female (circles) patients.

A similar analysis was performed to investigate the influence of age and gender on auditory function. First, differences of pure-tone air conduction thresholds relative to the 50 % percentile of age- and gender-matched ISO 7029 control data were computed for the five tested frequencies (0.5, 1, 2, 4, 6 kHz). These values were then averaged separately for each ear to obtain a unilateral measure of auditory function. As for vestibular function, age and gender significantly (two-way ANOVA: $p < 0.01$) influenced auditory function, with a decline of auditory function with age (or duration of disease) and more reduced function in male patients, as shown in Fig. 4B. While all semicircular canals in Fabry patients showed similar ($p > 0.05$) impairment (Fig. 4C), auditory deficits

Fig. 4 Differences of VOR gains obtained by search-coil head impulse testing along the three ipsilateral SCC of each ear in every patient relative to grand average of unilateral gains in healthy controls (**A, C**) and differences of pure-tone air conduction thresholds relative to ISO 7029 (**B, D**) in males (squares) and females (circles) patients at baseline examination. **A** Average VOR gain deficits (error bars: ± 1 SD) plotted at different age intervals; **C** as **A** but plotted for individual SCC. **B** Average pure-tone air conduction thresholds relative to 50th percentile of ISO 7029 (error bars: ± 1 SD) plotted at different age intervals; **D** as **B** but plotted for individual frequencies. *HSCC* horizontal SCC; *ASCC* anterior SCC; *PSCC* posterior SCC. Note that impairment of auditory function was significantly greater at higher frequency and at higher age, whereas vestibular function was significantly more reduced at higher age, but with no preference for a specific SCC



were significantly ($p < 0.01$) different among tested frequencies with largest differences at high frequencies (Fig. 4D).

Fig. 5 illustrates the effect of ERT on overall vestibular and auditory function. As for Fig. 4, only results from head impulse testing were considered for vestibular function. Overall vestibular function of a patient was defined as the average of VOR gains obtained by head impulses along the six semicircular canal directions (Fig. 5A). Likewise, the overall auditory function of a subject was defined as the average of hearing thresholds at 0.5, 1, 2, 4, and 6 kHz of both ears, whereby age- and gender-correction of hearing thresholds were computed by subtracting the age- and gender-matched 90th percentiles at each frequency before averaging (Fig. 5B).

Patients were divided into two groups depending on whether the overall VOR gain (Fig. 5A) or the overall hearing threshold (Fig. 5B), respectively, was within the normal range (group_N, triangles) or reduced (group_R, circles) relative to healthy subjects. At baseline examination, i. e. prior to ERT administration, average overall VOR gains of group_R were not significantly

different between males and females although overall VOR gains of females were less reduced than those of males (average overall gains for male 0.59 ± 0.09 , for female 0.61 ± 0.08 ; unpaired t-tests: $p > 0.05$; data not shown). In contrast, for pure tone audiometry, the average overall hearing thresholds for group_R at baseline were significantly different between male and female patients with hearing thresholds in females less impaired than in males (average overall hearing thresholds for male $47.3 \text{ dB} \pm 35.6$, for female $21.7 \text{ dB} \pm 10.9$; unpaired t-tests: $p < 0.05$; data not shown). Overall VOR gains and hearing thresholds at baseline in group_N were not significantly different between male and female patients (unpaired t-tests: $p > 0.05$; data not shown).

Because number of female patients receiving ERT ($N = 14$) was small, data of male and female patients were pooled for further analysis. Pooled data of group_N (triangles) and group_R (circles) were then partitioned into baseline examination (period I, i. e. prior to ERT administration) and according to the time passed from the beginning of the ERT to the date of ex-

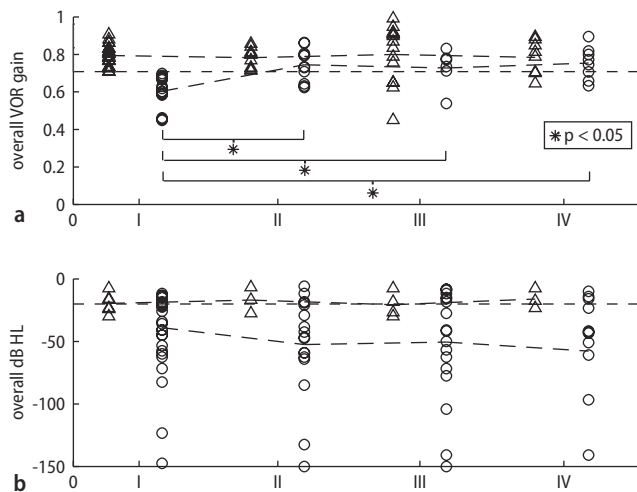


Fig. 5 Average of overall VOR gains (error bars: \pm 1SD) for search-coil head impulses (**A**) and overall hearing thresholds (error bars: \pm 1SD) for pure tone audiometry (**B**) at baseline and during enzyme replacement therapy (I: baseline examination, i. e. prior to ERT; II: 1 day – 1.5 year; III: 1.5 year – 3 years; IV: 3 years – maximal 5 years). Data from males and females are pooled. Triangles: patients with normal values (group_N). Circles: patients with reduced values (group_R). Asterisks: significant ($p < 0.05$) differences of average VOR gains in group_R between periods I and II, I and III as well as I and IV. Note that here only patients receiving ERT were included in baseline examination (N = 38; males: N = 24)

amination (period II: 1 day – 1.5 years; period III: 1.5 years – 3 years; period IV: 3 years – maximal 5 years; dashed lines connect average of corresponding groups; dashed horizontal line: lower limit of data from healthy subjects). For group_N, no significant change in both average overall VOR gain (Fig. 5A) and average overall hearing threshold (Fig. 5B) was noted during 60 months (ANOVA: $p > 0.05$). In contrast, average overall VOR gain differed significantly among the periods in group_R (ANOVA: $p < 0.01$). Specifically, multiple comparison revealed a significant ($p < 0.05$) vestibular improvement during the first 1.5 years of ERT (Fig. 5A). Thereafter, overall average VOR gain did not significantly change.

For auditory function, no significant changes of average hearing thresholds in group_R were observed during 60 months, although a slight tendency for further deterioration was visible (Fig. 5B). The same analysis as for overall hearing thresholds (see Fig. 5B) was repeated for single frequencies (0.5, 1, 2, 4, 6 kHz), average high frequency (4 and 6 kHz), and average low frequency (0.5 and 1 kHz). In these frequency-specific analyses, we also did not observe any significant changes in both group_N and group_R during ERT (data not shown). Finally, since in baseline examination, hearing thresholds of female patients differed significantly from male patients, all above analyses were repeated for male patients only. Again, no significant changes of auditory function in group_N and group_R were observed during ERT (data not shown).

In summary, ERT in Fabry patients led to a significant

improvement of vestibular function, which took place within the first year of treatment, while auditory function did not significantly change within the first five years of ERT.

Discussion

Our study confirms the high prevalence of both progressive hearing and vestibular loss in patients with Fabry disease and presents detailed analysis on the association between auditory and vestibular deficits before and during treatment with enzyme replacement therapy (ERT). Sensorineural hearing loss was observed in 88% of males and 86% of females and comprised all frequency ranges. Hearing loss was significantly influenced by age and gender. In particular, age-corrected auditory function was more impaired at higher age and deficits were greater in male than in female patients. In addition, auditory function differed significantly among tested frequencies with largest deficits at high frequencies. Vestibular deficits were present in 80% of males and 77% of females. As in auditory function, vestibular function was significantly more impaired in males and at higher age.

The high prevalence of vestibular deficits in our Fabry patients clearly differs from reports of previous studies [9, 29]. We believe that our finding is most likely due to the higher sensitivity of the search-coil head impulse test in detecting vestibular hypofunction compared to caloric irrigation [37]. In fact, only about 21% of our patients showed vestibular abnormalities when assessed by caloric irrigation. This relatively low percentage of caloric abnormality agrees with results from the previous studies [9, 29]. Two factors may explain why patients with Fabry disease show vestibular hypofunction more frequently when evaluated with search-coil head impulse testing compared to caloric irrigation: 1) The canal paresis factor, which is used to quantify caloric irrigation becomes pathological only if vestibular damage is asymmetric; in other words, the canal paresis factor is insensitive to roughly bilateral vestibular hypofunction. Head impulses, however, show that bilateral vestibular damage is not uncommon in Fabry patients (see Fig. 2). 2) Typically, the recovery of the vestibulo-ocular reflex (VOR) is frequency-dependent and incomplete at higher frequencies and accelerations [28, 30, 31]. While in patients after vestibular neuritis or vestibular neurectomy the low and medium frequency VOR, as assessed by turntable testing or caloric irrigation, is centrally compensated within several weeks, the high-frequency VOR, as assessed by head impulse testing, remains deficient even after many years [1–3, 8, 17, 20, 23, 37, 38]. As an additional factor we cannot exclude the possibility that high vestibular frequencies are more vulnerable to the pathological processes of Fabry dis-

ease than low vestibular frequencies. The fact that, in our study, all Fabry patients with pathological caloric irrigation had reduced head impulses as well and were more than 50 years old might support this hypothesis.

The location of vestibulo-cochlear damage in Fabry disease is not known. Possible sites are the vestibulo-cochlear labyrinth, the eighth cranial nerve or the root entry zone of the eighth cranial nerve. We speculate that the impairment is most likely located within the vestibulo-cochlear labyrinth, since the majority of Fabry patients showed no specific lesion pattern, as one would expect if lesions were proximal of the labyrinth along the superior (i. e. concomitant anterior SCC and lateral SCC deficits) or the inferior (i. e. concomitant posterior SCC and auditory deficit) branch of the vestibular nerve or labyrinthine artery [12]. We emphasize, however, that with our functional methods, we are not able to determine whether neural (including hair cells) or vascular structures within the labyrinth are affected in Fabry disease. Histological findings by Schachern et al. in temporal bones of two patients with Fabry disease suggest, on the basis of glycosphingolipid accumulation in the stria vascularis and in the spiral ganglion cells, that the etiology of cochlear lesions at the level of the hair cells is primarily of vascular origin [35]. A recent audiometric study by Ries et al. also comes to the conclusion that the auditory deficit is due to a cochlear impairment [34].

The effect of enzyme replacement therapy (ERT) was analyzed for vestibular and auditory function at follow-up examinations over five years. Previous studies in patients after vestibular neuritis and neurectomy have shown that unilateral vestibular deficits also influence the vestibulo-ocular reflex towards the contralateral healthy side by central mechanisms [23, 31]. Therefore, to investigate vestibular function during ERT, we averaged the vestibulo-ocular responses along the six semicircular canals for each patient. For comparison, the same binaural averaging was done for auditory function. During ERT over 60 months, auditory function did not significantly change in our patients, i. e. there was no indication for recovery, but also no indication for deterioration. So far, three other studies have reported on auditory function under ERT. While Conti et al. did not see an improvement during the first 12 months [9], Hajioff et al. found a significant decrease of sensorineural hear-

ing loss in the high frequency range after 18 months [15]. Hajioff et al. three years later found in the Fabry Outcome Survey a significant decrease of sensorineural hearing loss over all frequencies after 12 months [16]. A comparison between our and the other studies should only be done with caution because of different analytical methods. Conti et al. and the Fabry Outcome Survey study excluded extreme audiometric frequencies when calculating the amount of hearing impairment, while Hajioff et al. focused on the high frequency hearing impairment and averaged the hearing thresholds at 4 and 8 kHz. Our study provides evidence that the overall auditory function (average over all hearing thresholds in both ears) as well as the high-frequency auditory function (average of hearing thresholds at 4 and 6 kHz in both ears) remains stable during ERT. Thus, to date whether or not auditory function improves under ERT is still not conclusively answered.

In contrast to auditory function, the vestibular function in its high-frequency range (assessed by head impulse testing) significantly improved during the first one and a half years of ERT and remained unchanged thereafter. In a preliminary study, we reported on the effect of ERT on vestibular function as tested by head impulses in a much smaller population of Fabry patients. There we found a tendency of vestibular recovery within the first 12 months; these results, however, were not statistically significant [32]. With about twice the number of Fabry patients in the present study the vestibular improvement turned out to be significant.

In conclusion, we have demonstrated that in patients with Fabry disease vestibular deficits occur as frequently as auditory deficits. Functional tests support the hypothesis that the vestibular and auditory systems are mainly affected within the labyrinth, probably at the level of the hair cells. For the detection of vestibular deficits the search-coil head impulse test is more sensitive than caloric irrigation. Finally, ERT significantly improves the vestibular function in its high-frequency range, while the auditory function is at least stabilized.

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Head-impulse testing in Fabry disease – vestibular function in male and female patients

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Aim: To study the prevalence of peripheral vestibular deficit in male and female patients with Fabry disease and to assess the effect of enzyme replacement therapy (ERT) on peripheral vestibular function using quantitative head-impulse testing. **Methods:** Using dual search-coils the vestibulo-ocular reflex during rapid rotational head thrusts to both sides was recorded in 21 patients (13 male, 8 female) with Fabry disease prior to ERT initiation. ERT consisted of infusions of gene-activated human α -galactosidase A (agalsidase alfa; Replagal[®]) every 2 weeks at doses of 0.2 mg/kg. Eight patients were tested again approximately 6 and 12 months after the initiation of ERT. **Results:** At baseline examination, 15 of the patients with Fabry disease (71%; 11 males, 4 females) showed reduced peripheral vestibular function. The deficit was unilateral in nine patients (3 females) and bilateral in six patients (1 female). The severity of the vestibular deficit was not significantly different between male and female patients. After 12 months of ERT, the average vestibular deficit on the weaker side tended to improve; however, the change was not significant ($p = 0.10$).

Conclusion: Fabry disease affects peripheral vestibular function in both male and female patients. Females seem to be affected less frequently than males, but, on average, vestibular deficits are not different between the two groups. To confirm or reject the tendency for vestibular improvement during ERT, more patients need to be tested and longer follow-up periods are required.

Key words: Enzyme replacement therapy, Fabry disease, vestibular function, vestibular-ocular reflex

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Fabry disease is an X-linked lysosomal storage disorder due to deficient activity of the enzyme α -galactosidase A (α -Gal A) (1). The resultant intracellular accumulation of globotriaosylceramide and related glycosphingolipids, particularly in the vascular endothelium, leads to renal, cardiac and cerebrovascular manifestations. In patients with very low enzyme activity, progressive glycosphingolipid accumulation leads to early death secondary to renal failure, stroke or myocardial infarction. Although Fabry disease predominantly affects males, females may also show manifestations of the disease due to random X-chromosome inactivation. Until recently, management has been symptomatic, consisting of non-specific treatments for cardiac, renal and cerebrovascular complications. Since enzyme replacement therapy (ERT) with human α -Gal A has been made available, several studies have shown clearance of storage material and even reversal of some of the signs of the disease (2, 3).

The main neurological manifestations in patients with Fabry disease consist of cerebrovascular abnormalities (ischaemic or haemorrhagic lesions), episodic

painful crises (usually highlighting the clinical onset of disease), constant acroparaesthesias and symptoms arising from the involvement of structures innervated by the autonomic nervous system (4, 5). Some patients also report vertigo. To date, it is unclear to what extent vertigo in Fabry disease is indeed of vestibular origin; that is, whether presumed vestibular dysfunctions are localized along peripheral or central vestibular pathways. On the basis of diminished ocular responses upon caloric (reduced peak slow-phase eye velocity) and turntable (reduced gain and time constant of nystagmus) testing, Morgan et al. (6) suggested that, at least in part, the vertigo in patients with Fabry disease is due to peripheral vestibular involvement. Both caloric and turntable testing, however, have their limitations. While caloric testing provides only a non-physiological stimulation of the peripheral vestibular organ and may not be sufficient to identify a chronic peripheral vestibular lesion (7), turntable testing cannot quantify the function of both labyrinths separately.

The function of individual semicircular canals and their afferents can best be tested by the so-called head-

impulse test (8,9). Search-coil recording allows a quantitative assessment of the ocular response during head movements in the planes of individual semicircular canals (10). Using the search-coil head-impulse test, we studied the prevalence of peripheral vestibular deficits in male and female patients with Fabry disease, as well as the effects of ERT on vestibular function.

Materials and methods

Subjects

Twenty-one patients (13 male, 8 female; aged 22–71 years) who had been diagnosed with Fabry disease were included in the study. All patients were tested during a baseline examination before receiving ERT. Eight of the patients (5 male, 3 female; aged 22–54 years) were also assessed regularly during treatment. ERT consisted of infusions of gene-activated human α -Gal A (agalsidase alfa; Replagal[®]; TKT Europe – 5S, Danderyd, Sweden) every 2 weeks at a dose of 0.2 mg/kg (time range of treatment, 0–19 months). The comparison group consisted of 11 healthy subjects (6 men and 5 women; aged 25–59 years).

Informed consent was obtained from patients and control subjects after a full explanation of the experimental procedure. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki for research involving human subjects.

Quantitative head-impulse testing

Eye and head movements were recorded in a magnetic frame (Remmel type system, modified by A. Lasker, Baltimore, MA, USA) using dual search-coils (Skalar Instruments, Delft, The Netherlands), which were calibrated before each session (see Straumann et al. (11) for details). After anaesthetizing the conjunctiva with oxybuprocaine 0.4%, one search-coil was placed on the right eye around the cornea and the other was tightly fixed on the forehead with adhesive tape. Voltages were sampled at 16 bits at a frequency of 1000 Hz and stored on the hard disk of a computer.

During experiments, subjects were seated inside the magnetic coil frame (side length: 1.4 m). Care was taken to position the centre of the interpupillary line in the centre of the magnetic frame. Horizontal head impulses (amplitude, 20–40°; duration, 150–200 ms; peak velocity, ~300°/s; peak acceleration, ~10000°/s²) were applied by the investigator standing behind the subject. The directions of head impulses were pseudo-randomly intermingled; four to six head rotations were applied to each side. Subjects were instructed to always fixate straight ahead on a light dot 1.24 m away.

Data analysis

Digitized signals were processed using interactive

programs written in MATLAB[®] Version 6.5. The gain of the vestibulo-ocular reflex, g , was computed by:

$$g = 1 - \frac{\Delta e_s[h_0; h_1]}{h_1 - h_0}$$

where h_0 and h_1 are head-in-space positions, and Δe_s the difference between eye-in-space positions at $h_0 = 3^\circ$ and $h_1 = 7^\circ$. Traces of head impulses traversing the position interval $[h_0; h_1]$ were relatively straight. Median gains during head impulses to the right (G_R) and left (G_L) side were calculated.

Results

Typical eye and head traces during horizontal head impulses to both sides in a healthy subject and a patient with Fabry disease at baseline examination are shown in Fig. 1. In the healthy subject, gains were symmetrical, but not completely compensatory. In the patient with Fabry disease, gains were asymmetrical. In this example, the gain was reduced for head impulses towards the left. Overall, 15 patients with Fabry disease (71%) showed reduced gains. In six males and three females, gains for head impulses towards one side (left or right) were reduced, corresponding to a unilateral vestibular deficit. Gains in the remaining six patients, one of whom was female, were diminished towards both sides, equivalent to a bilateral peripheral vestibular deficit.

Average gains during head impulses towards the stronger and weaker side in male ($n = 13$) and female ($n = 8$) patients at baseline examination are plotted in Fig. 2. For head impulses towards the weaker side, the average gain in male patients was 0.59, which is reduced compared with healthy subjects. On the other hand, the average gain for head impulses towards the stronger side was 0.79, which is within the normal range. The difference in average gains between the two sides was significant (paired t -test: $p < 0.0001$). For female patients, the average gain on the weaker side was 0.68, which is almost normal, and towards the stronger side it was approximately 0.84. The difference in average gains between the two sides was significant (paired t -test: $p < 0.01$). There was no significant difference in gain between the male and female patients, comparing the stronger and weaker sides separately (unpaired t -tests: $p > 0.05$).

Gains before and during ERT are depicted in Fig. 3. Patients ($n = 8$) were tested at approximately 6 and 12 months after the initiation of therapy. For both male and female patients, no significant changes in average gain were noted after 12 months of ERT (paired t -test: $p = 0.10$). For the weaker side, gains transiently decreased within the first 6 months; however, there was a tendency for the gain to be higher than baseline after 12 months of treatment.

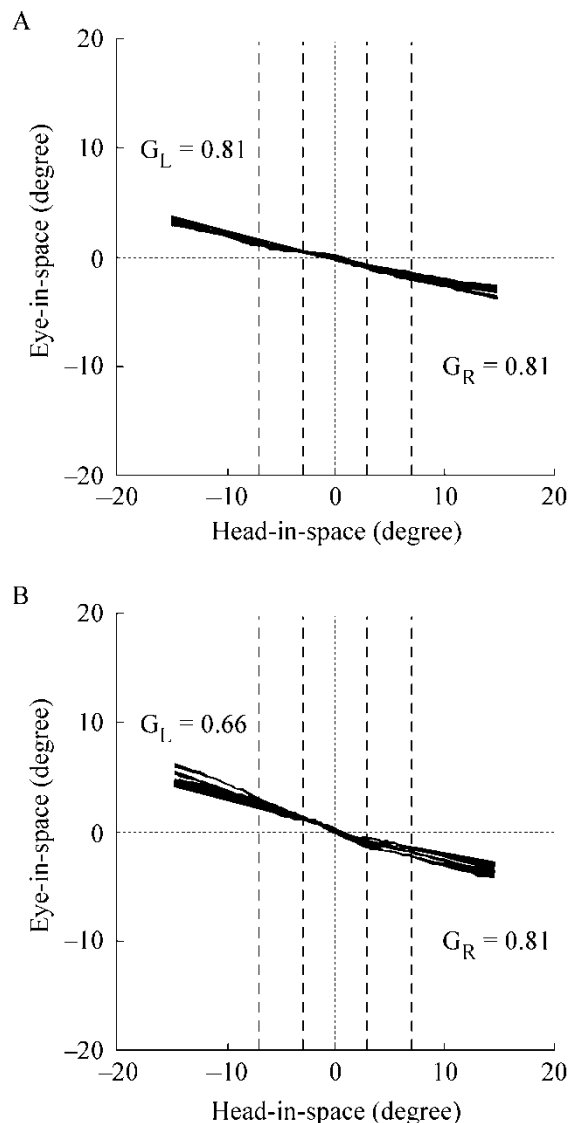


Fig. 1. Examples of horizontal head impulses in (A) a healthy subject, and (B) a patient with Fabry disease at baseline examination. If the vestibulo-ocular reflex were perfectly compensatory, traces would be parallel to the abscissa (head-in-space axis); if the vestibulo-ocular reflex were absent, traces would move on a 45° slope. G_R : median gain value for head impulses to the right; G_L : median gain value for head impulses to the left. Traces are clipped beyond 15° eccentricity of head-in-space. Dashed vertical lines indicate intervals used to determine the gains (see Methods).

Discussion

Previous studies have demonstrated deficits of the vestibulo-ocular reflex in the low and medium frequency range in patients with Fabry disease using caloric irrigation and turntable testing (6). Applying the search-coil head-impulse test, we found that the vestibulo-ocular reflex of patients with Fabry disease is deficient during high-acceleration head rotations.

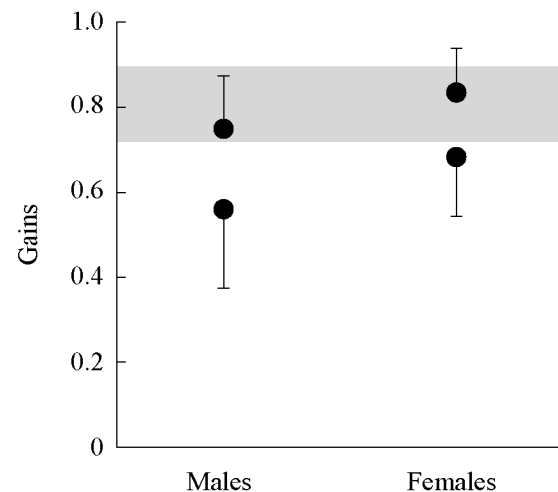


Fig. 2. Average gain values (error bars: ± 1 SD) during head impulses towards the stronger and weaker side in male ($n=13$) and female ($n=8$) patients at baseline. The shaded area corresponds to the average gain values of healthy subjects ± 2 SD.

Such vestibulo-ocular reflex hypofunction in response to high acceleration is highly suggestive of a peripheral vestibular deficit; that is, lesions within the vestibular labyrinth or along the primary vestibular neuron (7, 9, 10). Thus, it is plausible that decreased peripheral vestibular function accounts, at least in part, for the vertigo that patients with Fabry disease occasionally report. This finding, of course, does not preclude other causes of vertigo, for example, lesions along the central vestibular pathways as a result of abnormal cerebrovascular circulation (12, 13).

We can only speculate on the pathogenesis of the peripheral vestibular deficit in patients with Fabry disease, as measured ocular responses during head impulses do not allow us to distinguish between labyrinthine or vestibular nerve lesions. The auditory dysfunction of patients with Fabry disease suggests damage at the level of hair cells (6). Assuming a similar pathogenesis for the vestibular system, one may also find that hair cells in the ampullae of the semicircular canals are damaged. Alternatively, lipid deposition along vestibular neurons could impair electrical signal conduction. Such lipid depositions, however, are more prominent in the autonomic nervous system of patients with Fabry disease (14, 15). A further possibility is that endothelial glycosphingolipid deposition in vestibular arteries could lead to ischaemic lesions of both the labyrinth and the vestibular nerve.

Surprisingly, impairment to the peripheral vestibular system in patients with Fabry disease was not symmetrical. This finding may indicate that endothelial pathogenesis dominates, as asymmetry of ischaemic lesions is a regular finding in vascular diseases. Morphological studies will be needed to determine the

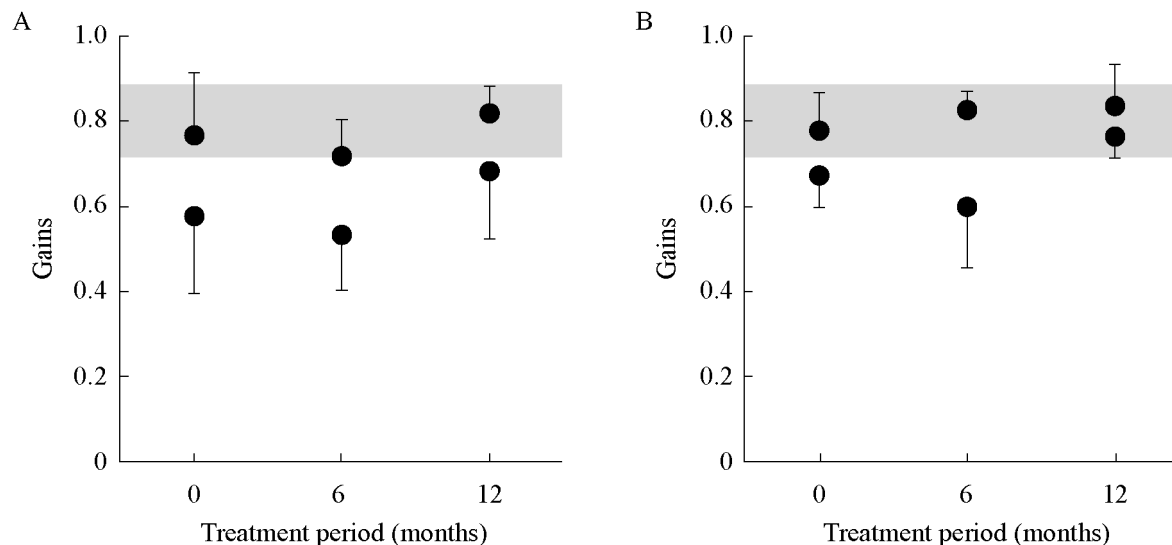


Fig. 3. Average gain values (error bars: ± 1 SD) for head impulses towards the stronger and weaker side in (A) male and (B) female patients at baseline and during enzyme replacement therapy.

exact causes of the peripheral vestibular deficit in patients with Fabry disease.

Previously, it has been suggested that females with Fabry disease also show signs of peripheral vestibular impairment, but so far the evidence has been limited (6). Our study provides clear evidence for peripheral vestibular deficits in female patients. As in male patients, peripheral vestibular deficits in female patients were mostly asymmetric. Although the severity of the clinical manifestations of Fabry disease in females is generally more variable than in males, ranging from asymptomatic to as severe as that in affected males, we found no significant difference in the severity of peripheral vestibular deficits between male and female patients.

Several studies have shown reversal of disease-related abnormalities in patients with Fabry disease given ERT (2, 16, 17). In our study, a subset of patients was tested before and 6 and 12 months after the initiation of ERT. In both male and female patients, there was a tendency for the weaker side to improve after 12 months of treatment. This improvement, however, was not significant. Possibly, with an increased number of patients, we may be able to demonstrate a significant improvement in vestibular function. However, as restoration of vestibular function, such as repair of nerves or hair cells, may be delayed relative to the clearing of the glycosphingolipid deposits, a longer follow-up period is also required.

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